DOES NOT CIRCULATE

VOL. 47 FEBRUARY, 1954 No. 2

# AMERICAN HEART JOURNAL

AN INTERNATIONAL PUBLICATION FOR
THE STUDY OF THE CIRCULATION

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Contents on Inside Cover

# American Heart Journal

## CONTENTS FOR FEBRUARY, 1954

### Original Communications


Page

The Effect of Heart Position and Rotation on the Cardiac Vector: An Experimental Study. L. Wolff, M.D., J. L. Richman, M.D., and A. M. Soffe, M.D., Boston, Mass. ..... 161

Normal Auricular Activation in the Dog's Heart. Paul Puech, M.D., Michel Esclavissat, M.D., Demetrio Sodi-Pallares, M.D., and Fernando Cisneros, M.D., Mexico City, Mexico ..... 174

Spread of Activation in the Left Ventricular Wall of the Dog. II. Activation Conditions at the Epicardial Surface. D. Durrer, M.D., and L. H. van der Tweel, M.S., Amsterdam, Holland ..... 192

Duration of the Q-T Interval During the Anoxemia Test. Dan C. Roehm, M.D., Ross C. Kory, M.D., Robert E. Mabe, M.D., Alexander S. Townes, M.D., and George R. Meneely, M.D., Nashville, Tenn. ..... 204

The Electrocardiogram in Hemorrhagic Fever. First Lieutenant Albert G. Smyth, Medical Corps, United States Army, and Colonel George M. Powell, Medical Corps, United States Army ..... 218

The Heart of the Rat With Special Reference to the Conducting System. Ravi Prakash, M.Sc., Ph.D., Ajmer, India ..... 241

Performance of Angiocardiography and Cardiac Catheterization as a Combined Procedure. Lieutenant Colonel Robert B. Dickerson, Medical Corps, United States Army ..... 252

Artificial Reduction of the Heart Effort. Th. Mottu, M.D., Geneva, Switzerland 270

The Effect of Lanatoside C on the Circulatory and Ventilatory Changes of Chronic Rheumatic Heart Disease With Mitral Stenosis. Frank D. Gray, Jr., M.D., and Frieda G. Gray, M.D., New Haven, Conn. ..... 282

The Spasmolytic Action of "Soluble Khellin-Nokhel." G. S. Barsoum, M.D., and M. R. Kenawy, M.D., Cairo, Egypt ..... 297


### Clinical Reports


Electrocardiographic Changes During Sensitivity Reaction to Penicillin. Sol. Glotzer, M.D., Brooklyn, N. Y. ..... 300

Bidirectional Ventricular Tachycardia Due to Digitalis Poisoning. Walter T. Zimdahl, M.D., and Charles E. Townsend, M.D., Buffalo, N. Y. ..... 304

Interventricular Septal Defect, Pulmonary Artery Aneurysm With Thrombosis, "Cyanose Tardive," and Paradoxical Systemic Arterial Embolizations. Dickinson W. Richards, M.D., and Isidor Cohn, M.D., New York, N. Y. .... 313


### Book Reviews


Book Reviews ..... 319



Vol. 47, No. 2, February, 1954. American Heart Journal is published monthly, by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917 at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, and its Possessions, per year $12.00; Canada $13.00; Foreign $13.50. Printed in the U. S. A.


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American Heart Journal

VOL. 47 FEBRUARY, 1954 NO. 2

## Original Communications

# THE EFFECT OF HEART POSITION AND ROTATION ON THE CARDIAC VECTOR: AN EXPERIMENTAL STUDY

L. WOLFF, M. D., J. L. RICHMAN, M. D., AND A. M. SOFFE, M. D.

BOSTON, MASS.

THE factors which influence the character of the cardiac vector in health and disease are heart position and rotation, myocardial hypertrophy, localized or generalized myocardial disease, and the anatomical and functional status of the intraventricular conduction system. The first two are the extrinsic, and the rest the intrinsic factors which, under a given set of conditions, determine the features of the cardiac vector. The effects of heart position and rotation are of great importance, not only in the normal heart, but in certain pathologic conditions in which characteristic alterations of heart position and rotation occur. Study of the extrinsic factors, therefore, offers a fruitful field for investigation.

Studies of this sort in man are beset with many difficulties because of the poor correlation between the anatomic and electric position of the heart, and the presence of numerous uncontrolled and unknown variables. Furthermore, changes in position and rotation of the heart are not easily accomplished in man, and the degree and kind of positional changes cannot be ascertained with certainty. To overcome these difficulties, a simple experimental method for studying the effect of heart position and rotation on the cardiac vector was devised.

### METHOD

A three-sided box was constructed from one-half inch plywood painted flat white (Fig 1). Each side measured 18 by 18 inches and corresponded to the frontal or coronal, sagittal, and horizontal planes of the thorax.[1] Cardboard protractors scaled to 360 degrees were superimposed on the inner surfaces of the box, and a diagram of the hexaxial reference system (after Bayley) was added to the side corresponding to the frontal plane of the thorax. The other vertical side corresponds to the sagittal plane, and the third side to the horizontal plane.

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This study was aided by a grant from the Massachusetts Heart Association.

Received for publication Aug. 5, 1953.

A length of 1/8 inch insulated copper wire was fashioned to form a QRS loop of any type which we desired to study and was soldered onto a 3/4 inch machined ball bearing. Alternate white and black bands were placed along the entire length of the centrifugal limb, and, in some of the models, at the terminal end of the centripetal limb as well. The black and white areas were clearly visible on

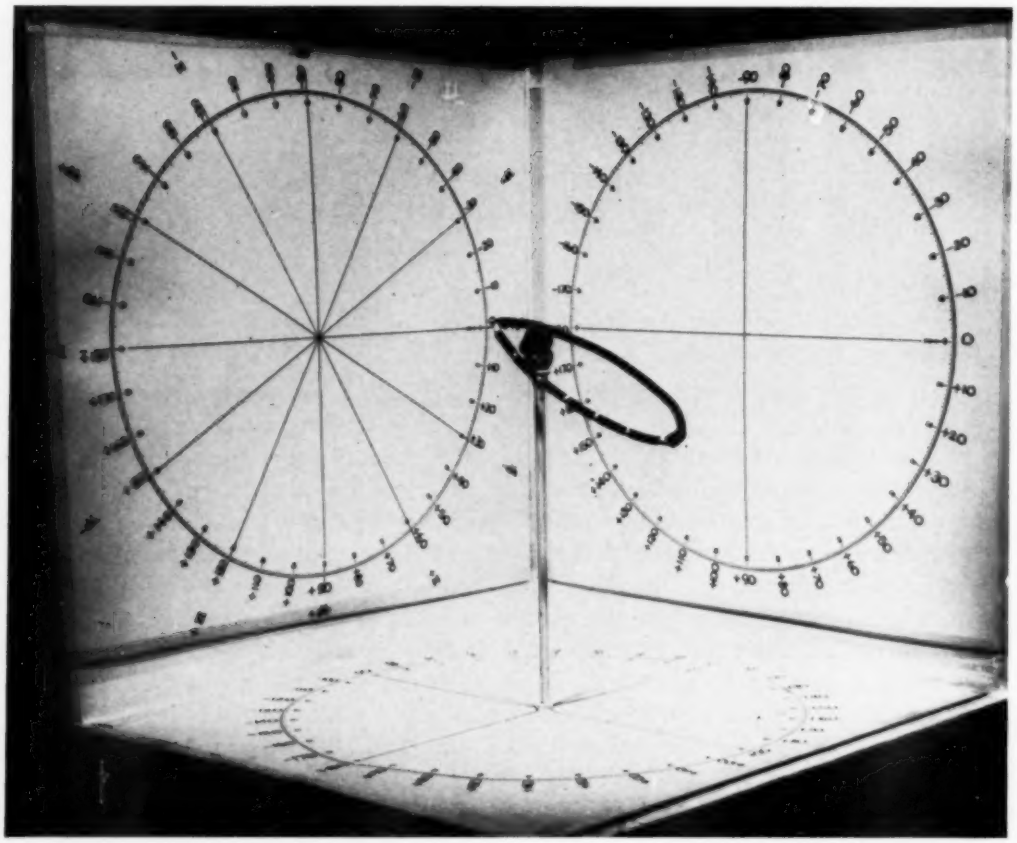


**Fig. 1.—Three-sided box with cardboard protractors scaled to 360 degrees applied to each side. A diagram of the hexaxial reference system of Bayley has been added to the side in the left background, corresponding to a frontal plane. The side in the right background corresponds to a sagittal plane, the floor of the box to a horizontal plane. A metal bar holding a wire model is inserted into the floor of the box.**

the photographs and served to identify the initial and terminal segments, and the centrifugal and centripetal limbs, of the loop. The wire model was placed into a small metal cup on the free end of a metal bar and was secured with a plastic adhesive compound. The other end of the metal bar was inserted into the base of the box. Thus, the upright metal bar supported the wire loop model in such a manner that the origin of the loop was exactly or almost exactly in the center of the three-sided box. The wire loop was then rotated on any one or a combination of three axes, corresponding to the transverse, anteroposterior, and long axes of the heart. The amount of rotation on each axis was accurately ascertained by direct inspection of the loop or of its photograph on the protractor background.

To obtain photographs, two goose neck lamps, each containing a 100-watt bulb, were adjusted so that the loop was flooded with light and as many gross shadows as possible eliminated from the background. A light meter provided the proper lens setting, and by focusing the lens on the wire model the latter, and not its shadow on the side of the box, was photographed.

A Foton 35 mm. camera was placed opposite the frontal plane of the box, then opposite the sagittal plane, and the corresponding views of the model were photographed. An Argus 35 mm. camera was suspended above the horizontal plane for the horizontal view. The center of the lens was 34 inches from the 0 point of the loop in each position. This distance was determined by trial and error to yield photographs which included the entire loop and the protractor background.

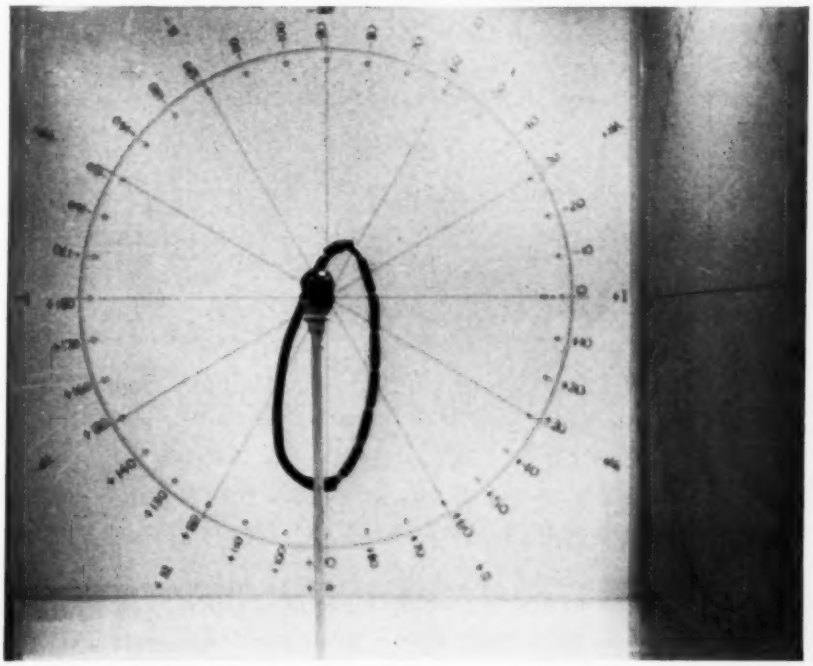


Fig. 2.—Wire model of a normal QRSsÊ loop. The long axis of the loop subtends an angle $\alpha$ of 90 degrees, and the loop is wide open on the frontal plane and inscribed clockwise. This position has been adopted as standard for describing the morphology of any loop and is not necessarily within the range seen clinically. The initial segment and the centrifugal limb are identified by the white markings. The protractor scaled to 360 degrees and the superimposed hexaxial reference system are clearly visible in the background corresponding to the frontal plane.

Prints of each photograph were made. In addition, tracings of each photograph were drawn by placing the film in a projector which cast an undistorted shadow of the loop and the protractor background on a sheet of white paper. These were then utilized to derive the scalar projections of the loops.[2]

Six wire-loop models were studied; they were constructed on the basis of our experience in spatial vectorcardiography using a modification of the orthogonal system of Duchosal.[2] These loops represent the normal vectorcardiogram (Fig. 2), uncomplicated complete right bundle branch block (Fig. 3), uncomplicated incomplete right bundle branch block (Fig. 4), incomplete right bundle

branch block complicated by right ventricular hypertrophy (Fig. 5), left bundle branch block (Fig. 6), and left ventricular hypertrophy (Fig. 7). Each wire-loop model was placed in various positions so that the long axis of the loop in the frontal plane subtended an angle with the line corresponding to Lead I (angle $\alpha$) between $-$ 60° and $+$ 90°. As a rule the loop was tipped slightly posteriorly, but in a few experiments it was tipped anteriorly. Various degrees of clockwise and counterclockwise rotation around the long axis of the loop were then effected in each position, and, at least two photographs in each of the three planes were obtained.

## RESULTS

Ninty-two experiments were done with the normal loop, 48 with left bundle branch block, 43 with complete right bundle branch block, 32 with uncomplicated incomplete right bundle branch block, 44 with incomplete right bundle branch block complicated by right ventricular hypertrophy, and 33 with left ventricular hypertrophy, making a total of 292 experiments. The spatial position of the initial and terminal segments of the loop, the relative spatial positions of the centrifugal and centripetal limbs, and the angular distance between the two limbs of the loop were found to vary in a characteristic manner with rotation of the loop around its longitudinal axis. The manner in which these features varied was characteristic for each position of the loop. Since the results are to be applied to the interpretation of vectorcardiograms the initial and terminal segments of the models may be compared to the initial and terminal QRS vectors, respectively, of the vectorcardiogram, and the relative spatial positions of the centrifugal and centripetal limbs to the direction of inscription of the QRS loops of the vectorcardiogram. These experiments will be reported in detail elsewhere, and only the general results will be given here.

Since the spatial characteristics of a loop, or any segment of it, vary with the position of the loop, a standard position has been selected for purposes of description. Unless stated otherwise, it may be assumed, when a loop or a part thereof is being described, that the long axis of the loop subtends an angle $\alpha$ of plus 90 degrees and that the loop is wide open and inscribed clockwise on the frontal plane.

*The Normal QRSÊs Loop.*—The normal QRS loop is a smooth, oval-shaped figure lying entirely, or almost entirely in one plane (Fig. 2). The initial vectors are small and point to the right, anteriorly, and up when the long axis of the loop subtends an angle $\alpha$ which is greater than zero and less than plus 90 degrees. If the long axis of the loop subtends an angle $\alpha$ of less than zero degrees, the initial forces point downward; when angle $\alpha$ exceeds plus 90 degrees the initial forces point to the left; such extreme positions are not seen in normal individuals. As angle $\alpha$ increases from zero to plus 90 degrees the initial forces point more and more superiorly, starting with no vertical displacement at zero degrees. In all positions and with sufficient rotation around the long axis of the loop to cause superimposition of the centrifugal and centripetal limbs on the frontal plane, and

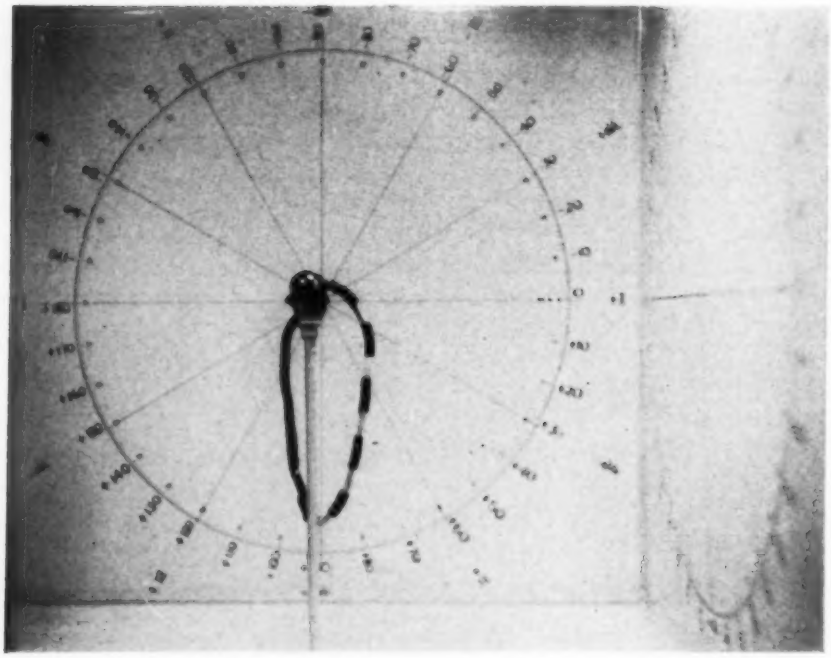
counterclockwise incription on the horizontal plane, maximum anterior displacement of the initial vectors occurs. The anterior displacement diminishes with either clockwise or counterclockwise rotation; clockwise rotation results in clockwise inscription, and counterclockwise rotation in counterclockwise inscription of the frontal loop. Rotation through 90 degrees in either direction produces wide open loops in the frontal projection and superimposition of the centrifugal and centripetal limbs on the horizontal plane.

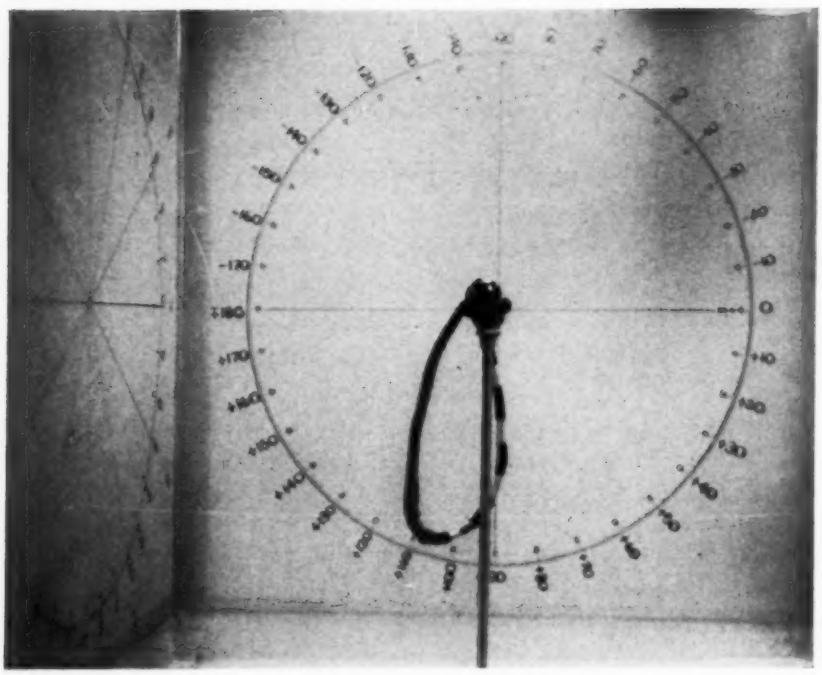
*Left Bundle Branch Block.*—The QRS loop in left bundle branch block is a smooth, oval-shaped figure similar to the normal loop, but differing from it in two respects: the initial QRS vectors are oriented anteriorly, inferiorly, and to the left in all positions and degrees of rotation comparable to those seen clinically; and the loop is twisted on itself so that it lies in several planes (Fig. 3). The sagittal QRS loop is inscribed in a clockwise manner, the frontal QRS loop counterclockwise. The direction of inscription of the horizontal loop depends on the degree of clockwise or counterclockwise rotation about the long axis of the loop, the direction being counterclockwise with clockwise rotation, and clockwise with counterclockwise rotation. Rotation of the loop about its long axis also produces characteristic changes in the spatial position of the initial vectors. Counterclockwise rotation of the horizontally placed loop increases the downward and decreases the anterior displacement of the initial vectors, and clockwise rotation does the opposite. If the loop is in a vertical position the initial forces are but slightly inferior; clockwise rotation increases their leftward, while diminishing their anterior, displacement and counterclockwise rotation does the opposite.

*Uncomplicated Right Bundle Branch Block.*—The QRSsÊ loop of uncomplicated right bundle branch block comprises two loops which are continuous with each other (Figs. 4A and 4B). The first is the larger of the two and is identical with the corresponding portion of the normal QRSsÊ loop. The second, and smaller part of the loop, is in a different plane, and is oriented superiorly, anteriorly, and to the right when the loop is in the standard position: clockwise and counterclockwise rotation around the long axis displaces the terminal loop anteriorly and posteriorly, respectively. The smaller loop is rightward and inferior when the loop as a whole is horizontal and the frontal projection is wide open and clockwisely inscribed; counterclockwise rotation displaces it posteriorly and clockwise rotation anteriorly. The initial vectors are similar in every respect to those of the normal QRS loop.

*Uncomplicated Incomplete Right Bundle Branch Block.*—There are no important differences in morphology of the QRSsÊ loop of uncomplicated complete and incomplete right bundle branch block, or of the effect of position and rotation on the initial and terminal vectors. The secondary loop in incomplete right bundle branch block is smaller than the corresponding loop in complete right bundle branch block (Figs. 5A and 5B).

A.

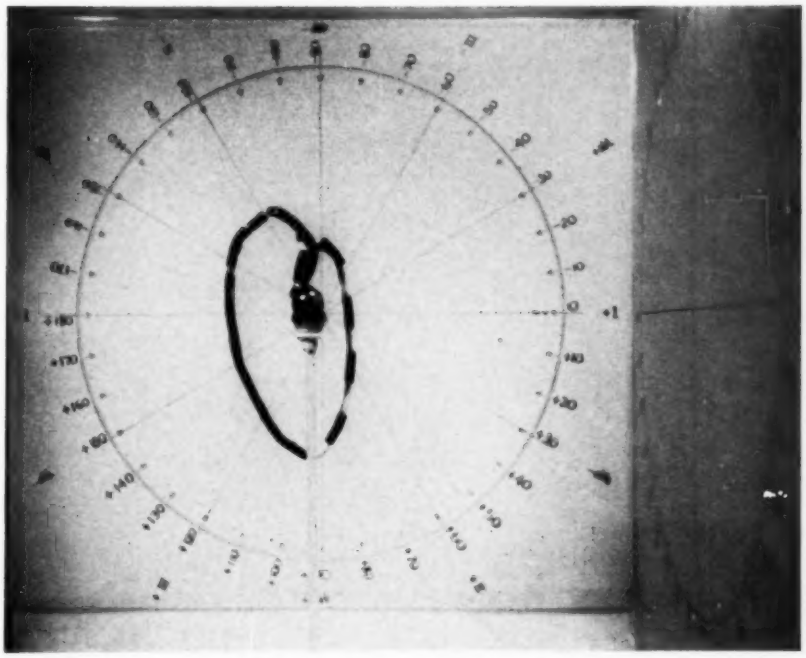


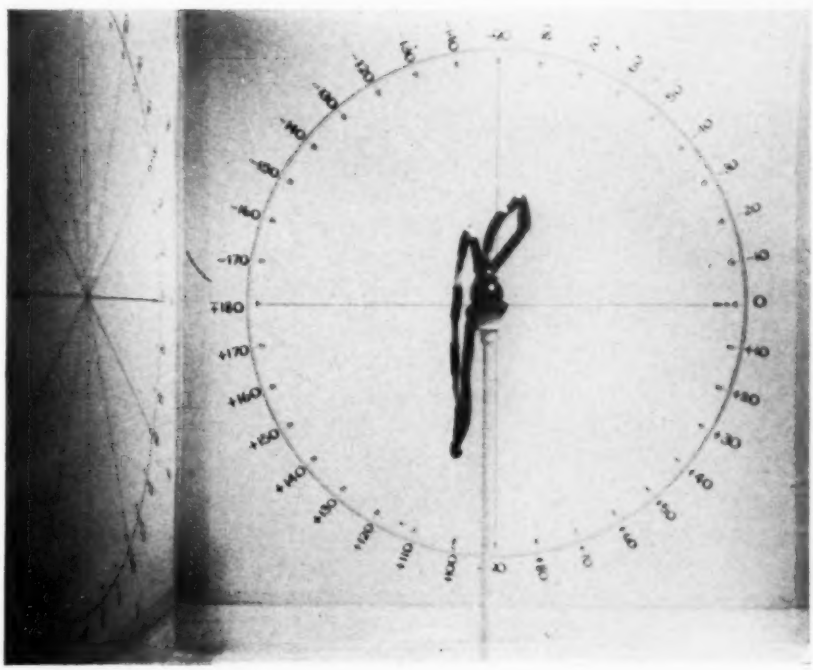


B.

Fig. 3.—A. and B. Frontal (A) and sagittal (B) views of a wire model (standard position) of a QRSsÊ loop in complete left bundle branch block. The centrifugal limb, identified by the white markings, bends anteriorly, then posteriorly, and the entire centripetal limb is posterior to the centrifugal limb. The initial segment goes to the left and downward. Placement of the model in relation to the metal bar shown in this figure is inevitable when certain positions and rotations are desired. When the initial and terminal segments are concealed by the bar, or when they are superimposed, the spatial position is accurately ascertained by direct inspection.

*A.*

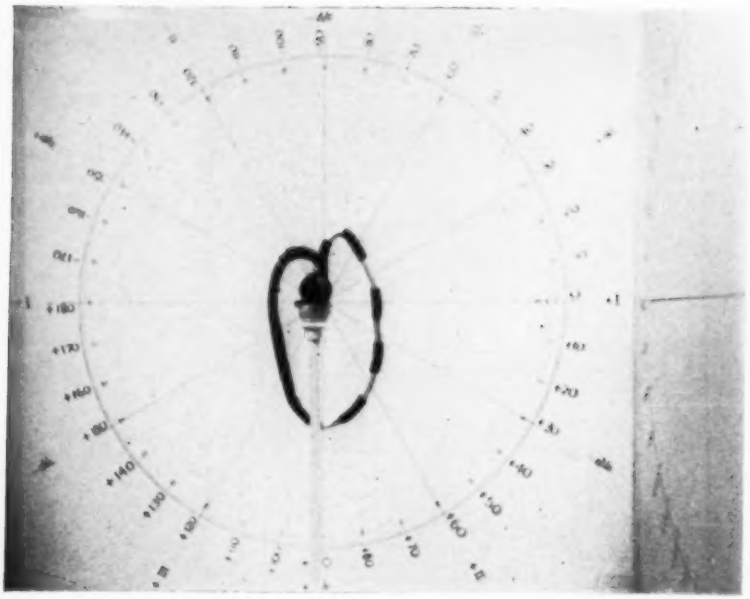


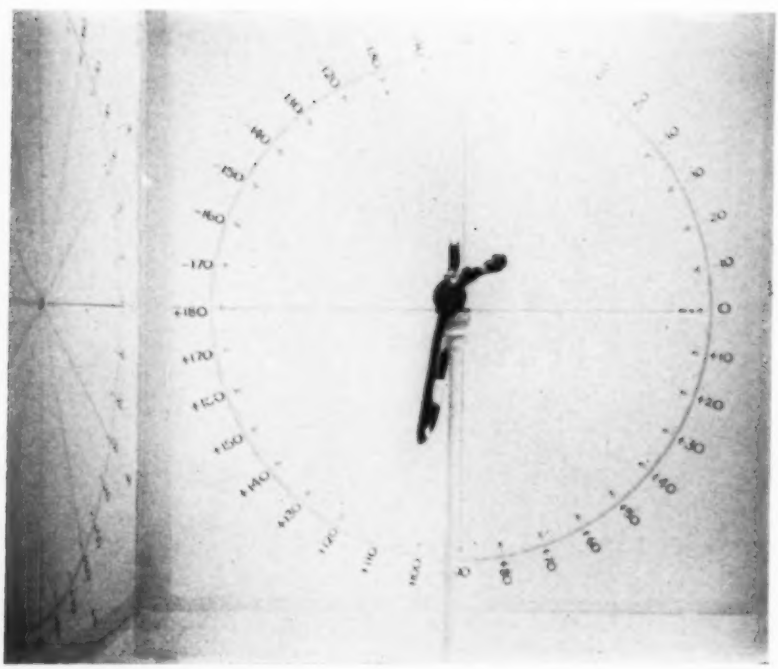


*B.*

Fig. 4.—A. and B. Frontal (A) and sagittal (B) views of a wire model in standard position (see legend for Fig. 2) of a QRSsÊ loop in complete, uncomplicated right bundle branch block. The first portion of the loop is identified by the wide white markings, the terminal portion by the three narrow white markings. The terminal, or secondary loop, is oriented to the right, anteriorly and superiorly.

A.

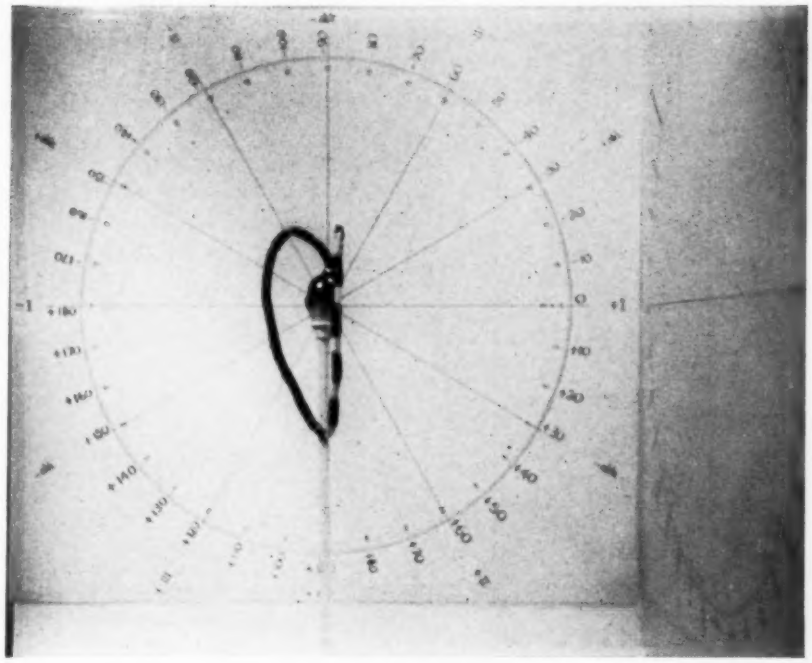


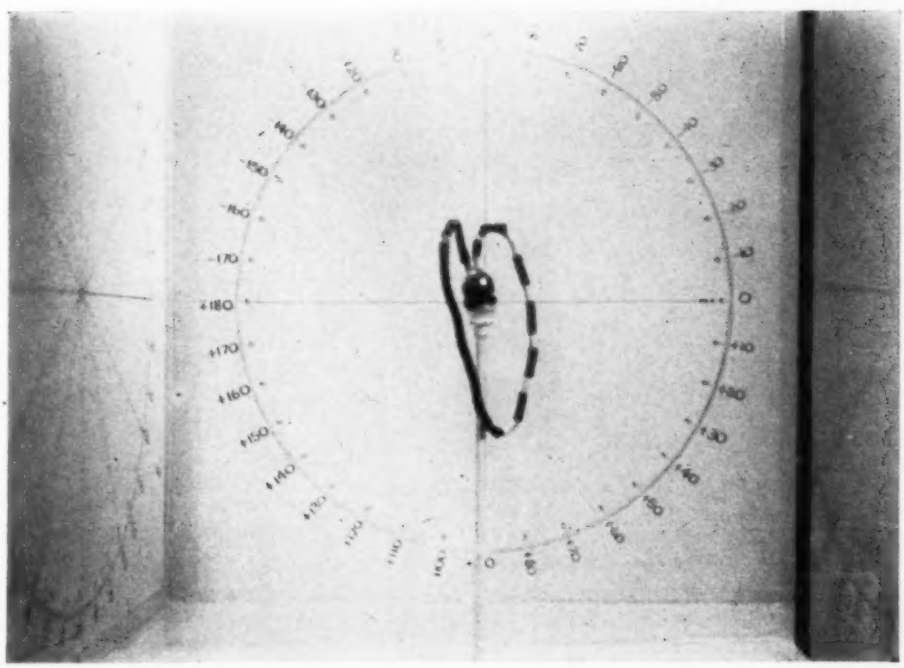


B.

Fig. 5.—A. and B. Frontal (A) and sagittal (B) views of a wire model (standard position) of a QRSsÊ loop in incomplete right bundle branch block. Compare with previous figure.

*A.*

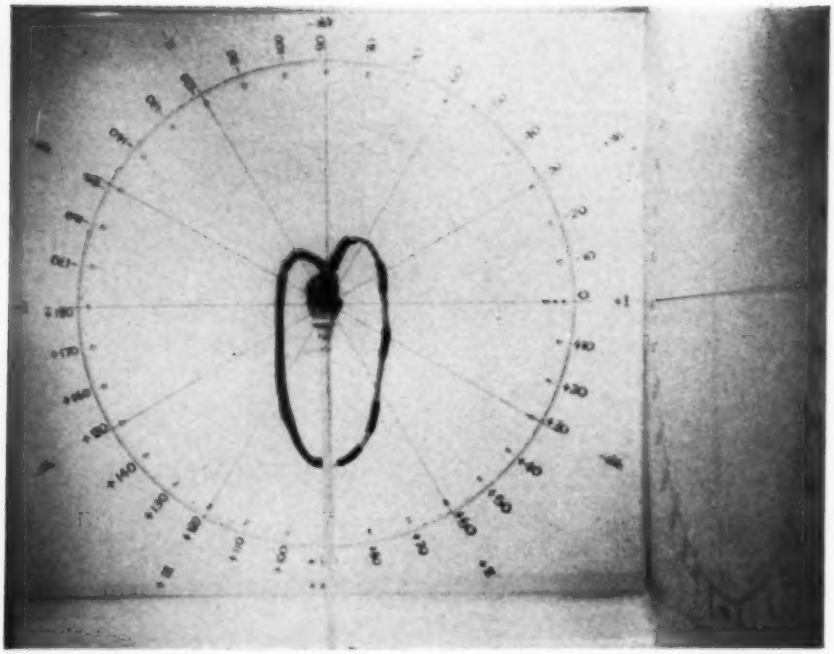


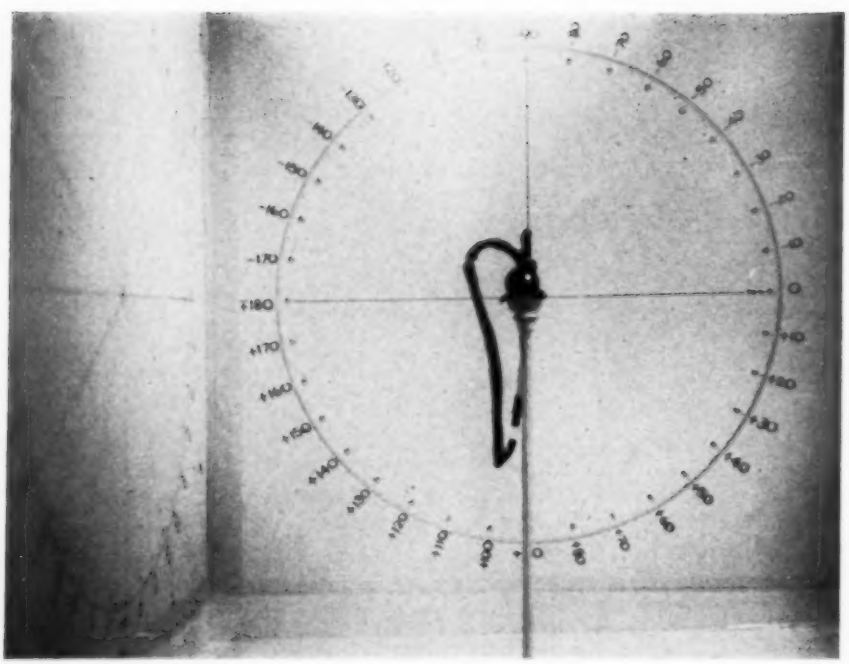


*B.*

**Fig. 6.—A. and B. Frontal (A) and sagittal (B) views of a wire model (standard position, apex tilted anteriorly) of a QRSsÊ loop in incomplete right bundle branch block complicated by right ventricular hypertrophy. Compare with previous figure.**

*A.*





*B.*

Fig. 7.—A. and B. Frontal (A) and sagittal (B) views of a wire model (standard position) of a QRSsÊ loop in left ventricular hypertrophy. The centrifugal limb, identified by the white markings, is similar to the corresponding limb of the normal loop in every respect. The centripetal limb deviates posteriorly in its terminal portion and rises above the point of origin, forming a small secondary loop

*Incomplete Right Bundle Branch Block Complicated By Right Ventricular Hypertrophy.*—The QRSsÊ loop of incomplete right bundle branch block complicated by right ventricular hypertrophy differs from that of uncomplicated incomplete right bundle branch block in only one respect; the QRS vectors, when viewed with the model in the standard position tend to deviate to the right, anteriorly, and superiorly, earlier in the QRS interval (Figs. 6A and 6B). There are, consequently, but minor variations in the orientation of the terminal vectors, and the initial vectors are identical in both conditions. The most important change is the tendency for reversal in direction of inscription of the horizontal and sagittal projections when the loop is rotated clockwise around its long axis.[3]

*Left Ventricular Hypertrophy.*—The QRSsÊ loop in left ventricular hypertrophy resembles both the normal loop and that of right bundle branch block (Figs. 7A and 7B). It is identical with the normal loop through most of its course, departing from it only after the beginning of the centripetal limb. The latter leaves the plane occupied by the earlier portions of the QRS loop, resembling right bundle branch block in this respect. However, when the loop is viewed in the standard position, the terminal part is oriented to the right, superiorly and posteriorly, compared to the rightward, superior, and anterior orientation in right bundle branch block. Therefore, the spatial position of the terminal vectors is different, and that of the initial vectors identical in both conditions.

## DISCUSSION

The method of studying the effect of heart position and rotation on the cardiac vector here described is simple and permits the exclusion of other factors which alter the cardiac vector. Visualization of the initial and terminal vectors is easily accomplished. However, there are theoretical objections to the method. Although it ignores the lack of homogeneity of the conducting medium and inequalities in distance of electrode positions from the O point, the wire model itself is constructed on the basis of vectorcardiographic planar projections which are influenced by these two factors. Also, the cardiac O point is variable and eccentric, whereas the wire model is fixed and central. Furthermore, the clinical planar projections, unlike the experimental planar views, are not necessarily mutually perpendicular.[1] Nevertheless, the frontal, sagittal, and horizontal views of the wire model obtained in our experiments are comparable to the corresponding projections of the spatial vectorcardiogram.

Our experimental observations have shown that the spatial orientation of the initial cardiac vectors is characteristic for various heart positions and degrees of clockwise or counterclockwise rotation. If these features are known, they may be utilized to determine heart position and rotation and to distinguish between the effects of these and intrinsic alterations of the cardiac vector. It has been noted, furthermore, that characteristic and diagnostic changes in the spatial position of the initial vectors take place in right and left ventricular hypertrophy indicating that clockwise rotation of the heart about its longitudinal axis occurs in right ventricular hypertrophy and counterclockwise rotation in left ventricular hypertrophy. Similarly; the initial vectors are characteristic in left bundle

branch block and may be used, not only to diagnose this conduction defect, but to recognize the degree and kind of rotation of the heart about its longitudinal axis. Therefore, the spatial position of the initial vectors may be used to distinguish extrinsic from intrinsic factors, and to differentiate the normal heart, right ventricular hypertrophy, left ventricular hypertrophy, combined ventricular hypertrophy, myocardial infarction, and left bundle branch block.

The spatial position of the terminal vectors is also helpful in determining heart position and rotation in those cases in which the QRSsÊ loop is altered by right bundle branch block or left ventricular hypertrophy, even when the initial vectors have been changed by localized myocardial disease, and, therefore, are unreliable for this purpose. The spatial orientation of the terminal vectors has proved valuable in the diagnosis of left ventricular hypertrophy when incomplete right bundle branch block is present, in the diagnosis of combined ventricular hypertrophy, in the differentiation of incomplete right bundle branch block from left ventricular hypertrophy, and in the differentiation of incomplete right bundle branch block from the normal, but unusually rotated loop.

The direction of inscription of each planar projection and a comparison of the width of the QRS loop in the various projections impart helpful clues to the presence of various degrees of clockwise or counterclockwise rotation of the loop about its long axis.

These experiments have helped to clarify the mechanisms which are responsible for the electric patterns seen in right and left ventricular hypertrophy. These are position and rotation, increased ventricular potentials, or bundle branch block, or any combination of these. It has become clear that the direction of inscription of the QRS loop depends on heart position and rotation, as well as upon intrinsic factors.

## SUMMARY

1. An experimental method has been devised for studying the effect of heart position and rotation on the cardiac vector.

2. The spatial positions of the initial and terminal vectors are characteristic for various heart positions and degrees of rotation. The width of the QRS loop in each projection indicates degree and direction of rotation. The direction of inscription of the QRS loop in various projections is related to the degree and kind of rotation of the loop about its longitudinal axis, as well as to intrinsic changes of the loop.

3. The spatial position of the initial vectors can be utilized to determine heart position, and for the differentiation of the normal heart, right ventricular hypertrophy, left ventricular hypertrophy, combined ventricular hypertrophy, myocardial infarction, and left bundle branch block.

4. The spatial position of the terminal vectors can be utilized to distinguish between left ventricular hypertrophy and incomplete right bundle branch block, and between the normal but unusually rotated heart and incomplete right bundle branch block.

5. The spatial position of the terminal vectors can be utilized to determine position and rotation of the heart, even when the initial vectors are not suitable for this purpose as a consequence of having been altered by localized myocardial disease.

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# NORMAL AURICULAR ACTIVATION IN THE DOG'S HEART

PAUL PUECH, M.D., MICHEL ESCLAVISSAT, M.D., DEMETRIO SODI-PALLARES, M.D., AND FERNANDO CISNEROS, M.D.

MEXICO CITY, MEXICO

THIS study of auricular activation has been carried out in our department with the purpose of completing previous studies concerning the activation of the septum and free walls of the ventricles.[1-3]

The electrical activity of the sinus node was first investigated by Wybauw[4], Lewis and associates[5,7,8] and Eyster and Meek[6,9,10] who considered as the normal pacemaker the point of primary negativity over the epicardial surface of the auricles. That point was located in a region which corresponds anatomically to the sinus node described by Keith and Flack.

Lewis' conclusions, based upon remarkable experimental work, are classic: from the sinus node the activation wave travels in radial manner, at an average rate of 1,000 mm./second; there are not specific ways of conduction. The last region activated is the tip of the left auricle (0.046 second). Nevertheless, the English investigator was unable to explore certain regions of the atria, and on the other hand, his records were obtained with distant bipolar leads (five to eight millimeters for the interelectrodal distance), through which it is difficult to determine the precise moment corresponding to the arrival of the activation wave to the site explored. These reasons induced us to repeat the study of the auricular activation, having at the same time the opportunity to know the morphology of the P wave in the epicardial auricular unipolar leads.

Recent works[11-19] upon intracavity potentials of the auricles in men's and dogs' hearts have not increased our knowledge on the activation process. High speed cinematography exploration[20] is undoubtedly of great value for the study of the mechanical phenomenon of the auricular contraction and propagation of the mechanical wave, but the results obtained through this method cannot be strictly applied to those based upon electrical recording.

## MATERIAL AND METHOD

The present study was done on thirty-seven dogs, well nourished and with a weight ranging from twelve to twenty kilograms. The anesthetic used was Nembutal by intraperitoneal injection, at a dose of thirty-five milligrams per kilogram of body weight.

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Received for publication Aug. 4, 1953.

*Technique.*—Under artificial respiration, the chest was opened through one of two techniques:

1.—Classic technique: medial incision and sternoclavicular disarticulation (used in 30 dogs).

2.—The technique recommended by Prinzmetal: transversal thoracotomy at the fourth intercostal space with bilateral subperiostic resection of the third, fourth, and fifth ribs. This technique allows a wider exploration of the lateral aspect of the left auricle as well as the right and left pulmonary veins. This method requires longer time, and it is a frequent cause of shock and arrhythmias (used in 7 dogs).

The pericardial sac is opened with a crossed incision and fixed to the thoracic wall.

*Electrodes*: The peripheral electrodes were connected by means of needles introduced under the skin of the animal.

The epicardial electrodes were made of very thin silver wire, twenty-five millimeters in length, forming a hook. All the surface, except the ends of the wire, was covered with isolating material in order to assure an epicardial contact of no more than one square millimeter. Some of these hooks were used as unipolar electrodes and others were placed together as close bipolar leads (the bipolar interelectrodal distance being no more than one millimeter.)

The electrodes used for the exploration of the interauricular septum were similar to those used in our department to study the activation process of the interventricular septum.[1]

*Regions of Easy Approach.*—

(a) The epicardial projection of the sinus node, located by exploring the sites where the earliest entirely negative deflection was obtained.
(b) Region between both venae cavae (Taenia terminalis).
(c) Right auricle and right auricular appendage.
(d) Right auriculoventricular groove.
(e) The tip of the left auricle.
(f) Region of the coronary sinus.
(g) Entrance of the left pulmonary veins.

In order to place the electrodes over the last two regions, the heart was first suspended and replaced afterwards in its natural bed.

*Regions of Difficult Approach.*—

(a) The right pulmonary vein's entrance.
(b) The lateral aspect of the left auricular appendage.
(c) The left auriculoventricular groove.
(d) The base of the left appendage.
(e) Anterior surface of both auricles.
(f) Posterior aspect of the left auricle.
(g) The interatrial septum.

The Prinzmetal technique permits a satisfactory approach for the first four regions, but up to the present time there were not eligible methods to explore the anterior auricular surface, in view of the presence of the great vessels and the

perivascular fat. Our method of approach to these regions is as follows: after a careful dissection of the perivascular fat, a ribbon is placed around the root of the aorta, which is pulled forward.

To explore the posterior aspect of the left auricle, which is the most difficult region to approach, a new technique was created since we found that the results obtained with esophageal leads, used at the beginning of our experiments, were not as accurate as those obtained with the direct method. Our technique consists of dissection of the pericardial folds and fatty tissue surrounding the pulmonary veins. A clamp is introduced between the pulmonary veins, and an intrapericardial passage is done. The electrodes are placed at the bottom of this passage in contact with the posterior wall of the left auricle.

For the study of the activation process of the interatrial septum Lewis' technique was not used since it permits only a limited exploration. With our method we avoid opening the atrial walls by introducing the special electrode described elsewhere[1] through different points of the auricular surface: at the base of the left appendix, the external wall of the right auricle, and the anterior aspect of both auricles. The tip of the electrode is fixed in the exploring site.

*Anatomic Control.—*

As soon as the heart was exposed, a drawing of the auricles was made, marking on it the different points explored as well as the interelectrodal distance. In order to control the exact location of the electrodes they were left in place to the end of the experiment; at this moment each electrode was replaced by a fine thread which permitted checking after formol-fixation of the specimen.

*Recording Methods.—*

Sanborn's Polyviso four-channel electrocardiograph was used for direct simultaneous recording. Standardization was made before and after each record was taken in order to avoid possible fluctuations of synchronization. The recording was done at the speed of fifty millimeters per second.

In all unipolar and bipolar tracings, the sinus node activity was simultaneously recorded as a control.

The conduction rate at the auricular surface was calculated in fourteen experiments using unipolar leads. The intrinsic deflection of each particular point was referred to the sinus node activation.

Proximal bipolar leads were used to determine precisely the arrival of the activation wave at each point. The vertex of the bipolar deflection (intrinsic phenomenon) was related to the sinus node deflection. The simultaneous tracings (unipolar and bipolar) showed that the arrival of the stimulus corresponds to the sharp fall of the intrinsic deflection, and not to the lowest point of the negative deflection. If in a unipolar lead a diphasic deflection was found, the activation moment corresponded, in most of the instances, to the middle part of the intrinsic deflection. When the tracings were predominantly positive, the activation moment corresponded to the inscription of the earliest part of the downstroke of the curve. A greater value was given always to the bipolar leads to determine the moment of depolarization.

## RESULTS

I.—*Right Atrial Activation* (Figs. 1 and 2 and Table 1).—

(a) *The pacemaker:* The electrical events of the pacemaker were manifested in a small area of the auricular zone, which represents a surface of a few square millimeters. On this region, pure negative deflections were obtained (point *1* of Fig. 1).* The first portion of the downstroke was inscribed rapidly (0.005 second); the upstroke was inscribed slowly and frequently showed slurrings and notchings.

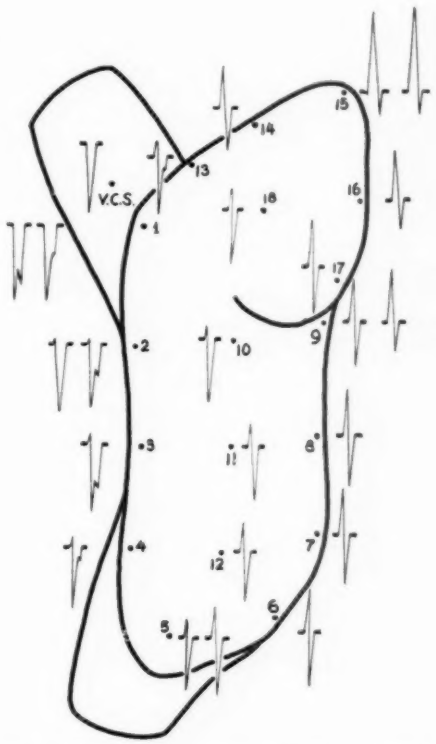


Fig. 1.—External aspect of the right auricular body and appendage. This figure shows the morphology of the unipolar leads at the different points explored.

The purely negative tracing and the rapid intrinsic deflection are characteristic of the sinus node activity. The earliest intrinsic deflection of the pure negative complex permits a clear distinction of the sinus activity from that of some areas in the auricles which may also give rise to pure negative complexes. It seems important to remark that if the exploring electrode is placed a few millimeters away from the epicardial projection of the sinus node head, a small initial positive deflection is always registered.

*In describing the morphology of the unipolar leads we always refer to the P wave.

TABLE I. TIMES AT WHICH ACTIVATION WAVE ARRIVES AT EPICARDIAL SURFACE OF DIFFERENT POINTS EXPLORED

| POINT EXPLORED | ACTIVATION TIMES (SEC.) | POINT EXPLORED | ACTIVATION TIMES (SEC.) | POINT EXPLORED | ACTIVATION TIMES (SEC.) | POINT EXPLORED | ACTIVIATION TIMES (SEC.) | POINT EXPLORED | ACTIVIATION TIMES (SEC.) |
|---|---|---|---|---|---|---|---|---|---|
| 2 | 0.0050*-0.0092†-0.0150‡ | 12 | 0.0200 | 23 | 0.0200-0.0250-0.0300 | 34 | 0.0400-0.0460-0.0750 | 45 | 0.0350-0.0449-0.0570 |
| 3 | 0.0100-0.0143-0.0250 | 13 | 0.0200 | 24 | 0.0200-0.0280-0.0320 | 35 | 0.0400-0.0450-0.0500 | 46 | 0.0350-0.0394-0.0450 |
| 4 | 0.0200-0.0252-0.0350 | 14 | 0.0250 | 25 | 0.0200-0.0262-0.0300 | 36 | 0.0350-0.0400-0.0500 | 47 | 0.0200-0.0217-0.0250 |
| 5 | 0.0340-0.0341-0.0400 | 15 | 0.0200-0.0277-0.0400 | 26 | 0.0400-0.0425-0.0450 | 37 | 0.0350-0.0394-0.0450 | 48 | 0.0100-0.0176-0.0200 |
| 6 | 0.0400-0.0417-0.0450 | 16 | 0.0250-0.0283-0.0350 | 27 | 0.0200-0.0326-0.0400 | 38 | 0.0350 | 49 | 0.0150-0.0150-0.0150 |
| 7 | 0.0270-0.0316-0.0450 | 17 | 0.0200-0.0237-0.0250 | 28 | 0.0200-0.0266-0.0300 | 39 | 0.0300-0.0316-0.0400 | 50 | 0.0170-0.0187-0.0250 |
| 8 | 0.0250-0.0340-0.0400 | 18 | 0.0100-0.0166-0.0250 | 29 | 0.0200-0.0260-0.0300 | 40 | 0.0200-0.0270-0.0400 | 51 | 0.0150-0.0188-0.0250 |
| 9 | 0.0250-0.0257-0.0350 | 19 | 0.0100-0.0150-0.0220 | 30 | 0.0180-0.0188-0.0200 | 41 | 0.0241-0.0250-0.0350 | 52 | 0.0150-0.0187-0.0200 |
| 10 | 0.0100-0.0160-0.0250 | 20 | 0.0150-0.0197-0.0250 | 31 | 0.0170-0.0235-0.0300 | 42 | 0.0250-0.0315-0.0370 | 53 | 0.0200-0.0217-0.0250 |
| 11 | 0.0170-0.0185-0.0200 | 21 | 0.0250-0.0316-0.0400 | 32 | 0.0200-0.0235-0.0250 | 43 | 0.0400-0.0481-0.0600 | 54 | 0.0270-0.0295-0.0300 |
| | | 22 | 0.0100-0.0175-0.0250 | 33 | 0.0400-0.0425-0.0450 | 44 | 0.0450-0.0521-0.0600 | 55 | 0.0300-0.0300-0.0300 |

*First value corresponds to minimal time obtained; †, second figure to the average time; ‡, third figure to the maximal time.

(b) *The sulcus terminalis:* This zone extends between both venae cavae and is marked on the atrial surface by a shallow depression known as Taenia terminalis. The body and tail of the sinus node correspond to this region. At the Taenia terminalis zone, the complexes recorded are of the rS type (points *2*, *3*, and *4*). The magnitude of the initial positivity tends to increase as the exploring electrode approaches the insertion of the inferior vena cava; nevertheless, the negativity is always the dominant deflection of the complex. The activation wave reaches the middle portion of the sinus node in about 0.0092 second (point *2*) and the tail of the node in about 0.0143 second (point *3*), (Figs. 1 and 2).

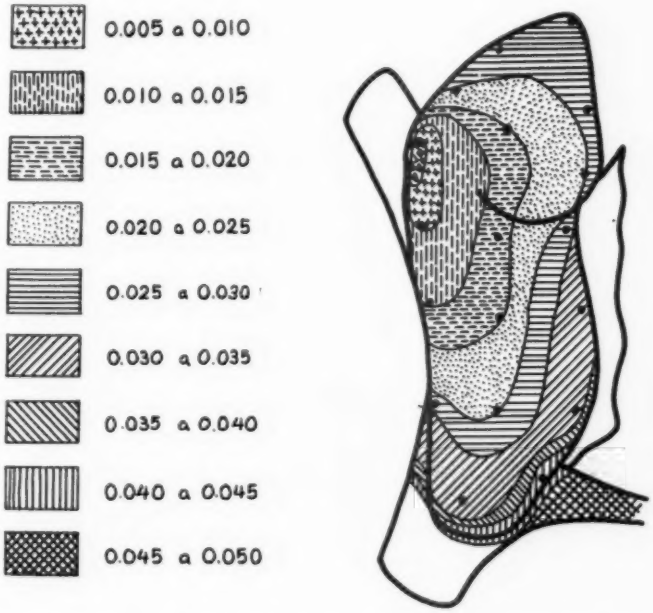


Fig. 2.—External aspect of the right auricular body and appendage. Spread of the electrical impulse at 0.005 second intervals. The reference value corresponds to the initial activity of the sinus node.

(c) *External aspect of the right auricle:* At the middle zone of this region, the morphology of the unipolar leads changes from above downward as follows: at the point of insertion of the auricular appendage (point *10*) the complexes are of the rS type (Fig. 1); at the middle and inferior areas (points *11* and *12*), the complexes tend to become diphasic, but the R deflection is of equal or lesser magnitude than the S deflection. The arrival of the activation wave takes place later below than above: point *10* is activated at 0.016 second after the sinus head, while point *12* is activated 0.004 second later. The complexes registered at the right auriculoventricular groove have an isodiphasic morphology (Fig. 1); however, in some instances a greater positive deflection may be recorded at the anteroexternal zone of the appendage insertion (point *9*). The average times of activation along the auriculoventricular groove are: 0.0257 second (point *9*), 0.034 second (point *8*), and 0.0316 second (point *7*).

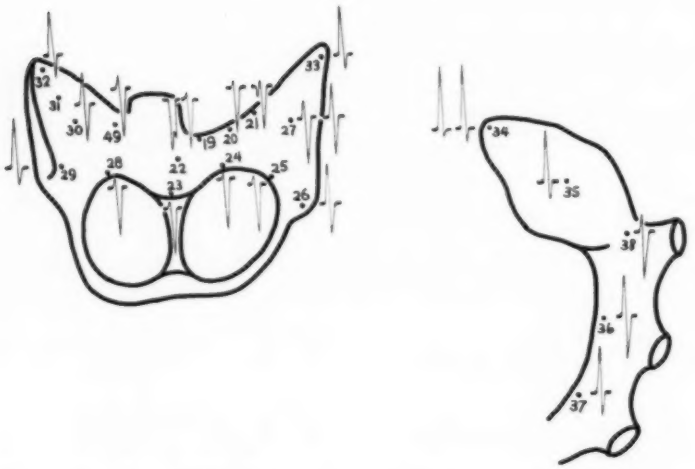


Fig. 3.—Drawing on the left represents the anterior aspect of both auricles. Drawing on the right corresponds to lateral aspect of the left auricular body and external surface of the left appendage. This figure shows the morphology of the unipolar leads at the different points explored.

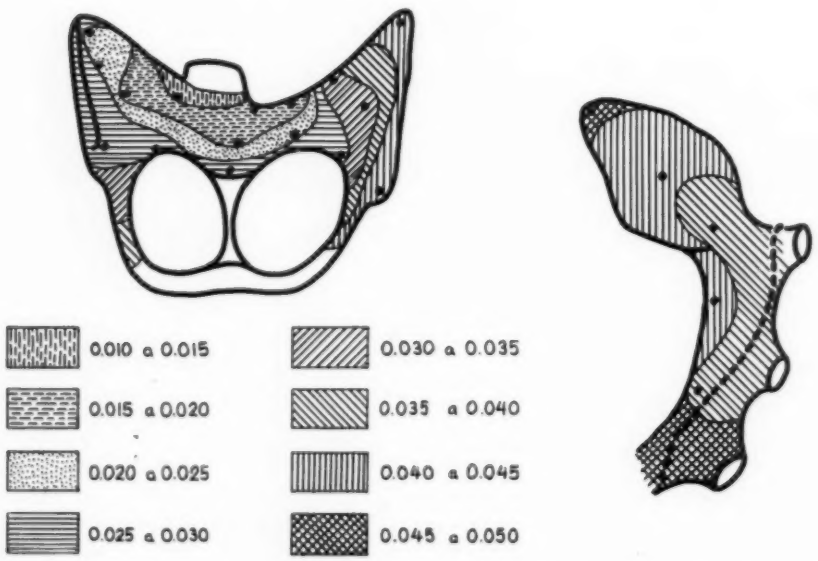


Fig. 4.—Drawing on the left represents the anterior aspect of both auricles. Drawing on the right corresponds to lateral aspect of the left auricular body and external surface of the left appendage. In this figure is shown the way of spread of the electrical impulse at 0.005 second intervals. The reference value corresponds to the initial activity of the sinus node.

(d) *Region of the inferior vena cava* (Figs. 1 and 2): On the external aspect of the inferior vena cava insertion (point *5*) the tracings are of the rS and RS type, and the activation takes place in about 0.0341 second; at the internal aspect of the vein the tracings are of the RS type (point *6*), and the time of activation is about 0.0417 second.

(e) *Right auricular appendage* (Figs. 1 to 4): On the superior border of the right auricular appendage, near the region of the sinus node (point *13*), and on the middle zone of the appendage (point *18*) the morphology found is rS. As the exploring electrode approaches the anterior border and the tip of the appendage, the morphology becomes diphasic with predominance of the positivity (Figs. 3 and 4). Thus, at the tip (point *15*), and at the angle of the appendage insertion (point *29*) a tall R deflection with a small S deflection were found. In some instances complexes were registered with a small Q wave, at both points. The activation takes place from below upward on the internal and external aspects of the right appendage, but the internal surface is activated earlier than the external surface. The last point of the appendage to be activated corresponds to the tip (0.0280 second).

(f) *Anterior aspect of the right auricle* (Figs 3 and 4): This auricular region is limited: above by the insertion of the superior vena cava, below by the tricuspid ring, externally by the insertion of the right auricular appendage, and internally by the projection of the interatrial septum. The complexes registered in this region are of the rS type, but at times QS complexes with an embryonic R deflection may be found; the activation occurs at 0.0150 second near the superior vena cava, and at 0.0266 second near the tricuspid ring (point *28*).

II.—*Left Auricular Activation* (Figs. 3 to 6, and Table I).—

(a) *Anterior aspect* (Figs. 3 and 4): Between the left and the right auricular anterior surfaces no definite external boundaries can be distinguished, and it is only the projection of the anterior insertion of the interatrial septum which permits this separation. Over all the anterior surface the complexes are of the rS type (points *19*, *20*, *24*, and *25*), and the activation varies from 0.0150 second to 0.0262 second.

(b) *Left auricular appendage* (Figs. 3 and 4): At the root of the left auricular appendage, the complexes registered are of the rS type (points *21* and *38*). The depolarization is evidently delayed over the entire zone: 0.0316 second (point *21*) and 0.0350 second (point *38*). At the internal region of the appendage the tracings are similar to those found at the internal surface of the right appendage. Over the external surface the morphology is Rs for the middle zone, and the amplitude of the S deflection diminishes as we explore places close to the tip of the appendage. The last point of activation is the tip of the appendage (0.0460 sec., point *34*).

(c) *Posterior aspect* (Figs. 5 and 6): Between the superior pulmonary veins (point *40*) the morphology found is rS, and the activation occurs at 0.0270 second. At the middle zone of the posterior aspect (points *41* and *42*) the complexes are isodiphasic, and the activation time is from 0.0241 to 0.0315 second.

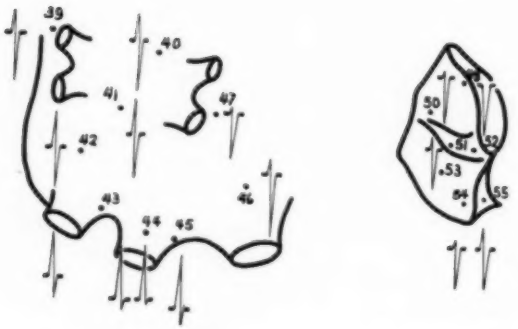


Fig. 5.—Posterior aspect of the left auricle and right aspect of the interatrial septum. Morphology of the unipolar leads at the different points explored.

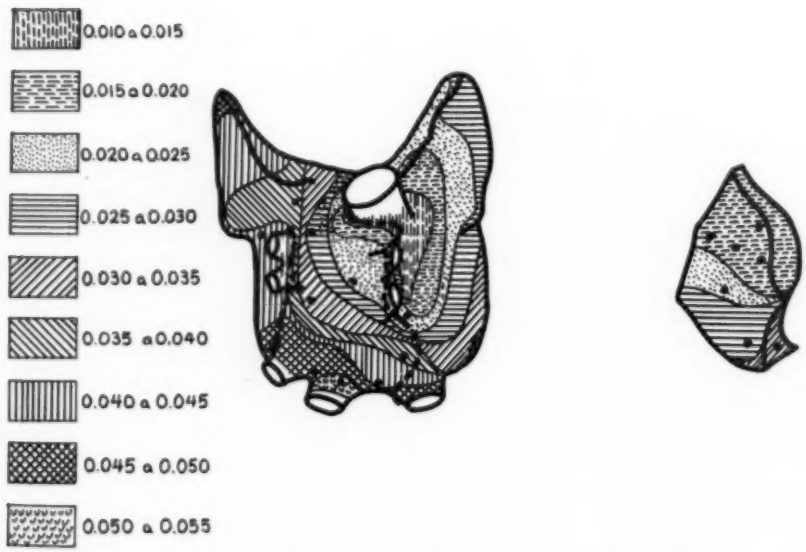


Fig. 6.—Posterior aspect of the auricles (left drawing), and right aspect of the interatrial septum. This figure shows the spread of the electrical impulse at 0.005 second intervals. The reference value is the initial activity of the sinus node.

(d) *Lateral aspect* (Figs. 3 and 4): It is a narrow zone located between the left auriculoventricular groove and the lateral pericardial reflection. In this region, in the upper zone (point *36*), the tracings are isodiphasic, and the activation appears at 0.0400 second. In the inferior zone (point *37*) the morphology is Rs, and the activation time is practically the same as that for the upper zone (0.0394 second).

(e) *Inferior aspect* (Figs. 5 and 6): This zone is located between the site of entrance of the inferior pulmonary veins and the auriculoventricular groove (points *43*, *44*, and *45*). In this region the complexes are of the Rs type. These points are the latest to be activated (from 0.0490 second to 0.0521 second). It is interesting to remark that at these zones as well as at the tip of the left auricular appendage, entirely positive complexes were never found.

III.—*Interatrial Septum Activation* (Figs. 5 and 6, and Table I).—

At the superior insertion of the septum (point *48*) the complexes found are of the rS type, or less frequently of the QS type. In the middle region (points *50*, *51*, and *52*), and at the inferior areas (point *53*), the morphology observed is also of the rS type. The activation takes place from above downward, and from the back forward. For the upper part the activation occurs at 0.0176 second; for the middle region at 0.0187 second, and for a lower zone at 0.0217 second. The last areas of activation (points *54* and *55*) are at the anteroinferior septal insertion (0.0295 second and 0.0300 second).

## STUDY OF THE GENERAL ACTIVATION PROCESS

The origin of the electrical auricular activity is located at the head of the sinus node. We have confirmed Lewis' observations that the site where the primary negativity is registered corresponds to the point of convergence of the muscular bands of the auricle, at the cava-auricular junction. Within the sinus node the propagation of the impulse travels rapidly from above downward, i. e., from the head to the tail, and it is more rapid than for the rest of the auricular muscle.

We have drawn a schematic representation of the spread of the activation wave at 0.005 second interval, on the auricular surface (Figs. 2, 4, and 6). Thus, we have found that the activation process over the external aspect of the right auricular body spreads, in general terms, in a radial form around the zone of the head and body of the sinus node. On the right auricular appendage the electrical impulse travels from below upward, and from the back forward. The anterior aspect of both auricles is activated from above downward, beginning around the superior vena cava, and ending at the tricuspid and mitral rings. The general activation of the left auricular body is from right to left, and from above downward. On the left appendage the impulse goes from below upward on both internal and external surfaces, but it is earlier in the former.

The activation time is about the same for the tip of the left appendage as for the posteroinferior region of the left auricle. But, in most of the cases, the points of later activation are located near the insertion of the inferior pulmonary veins. In fact, in seventeen of the thirty-seven dogs where simultaneous records were taken from the tip of the left appendage and from the inferior region of the left auricle, it was found that in fourteen instances the last region activated was that of the left inferior pulmonary vein entrance. In only three cases the activation was simultaneous.

TABLE II.* COMPARATIVE STUDY OF OUR RESULTS AND THOSE OBTAINED BY LEWIS

| REGIONS EXPLORED | RESULTS OBTAINED BY LEWIS | PERSONAL RESULTS |
|---|---|---|
| Intercaval Region | 0.0060–0.0139–0.0278 | 0.0100–0.0143–0.0250 |
| Interauricular Band Region | 0.0031–0.0126–0.0222 | 0.0100–0.0150–0.0220 |
| Base Interauricular Septum | 0.0255–0.0305–0.0442 | 0.0270–0.0295–0.0300 |
| Middle Portion Interauricular Septum | 0.0097–0.0305–0.0352 | 0.0200–0.0217–0.0250 |
| Tip of Right Auricular Appendage | 0.0141–0.0314–0.0487 | 0.0200–0.0277–0.0400 |
| Tip of Left Auricular Appendage | 0.0372–0.0446–0.0515 | 0.0300–0.0460–0.0550 |
| Inferior Vena Cava | 0.0218–0.0325–0.0543 | 0.0300–0.0341–0.0400 |
| Coronary Sinus | 0.0327–0.0412–0.0483 | 0.0350–0.0449–0.0570 |

*See Table I for legend.

The duration of the total activation time of both auricles averages 0.0521 second; however, there are variations from one dog to another. The minimal duration of the activation time was 0.0450 second, and the maximal 0.0600 second.* The variations in the global activation time do not interfere with the normal direction of the activation process already described.

We have studied the relation between the auricular activation and the P wave in Lead II (Fig. 7 and Table III).

In fifteen experiments Lead II was registered simultaneously with the sinus activity and with different epicardial leads. From these findings, drawings of the P wave have been made, which are similar to those of Wedd and Stroud[21], on

*We have excluded one case with a total activation time of 0.0750 second, in which an isolated conduction disturbance was observed on the left auricle.

TABLE III. RELATION BETWEEN INITIAL AND FINAL POINTS OF ACTIVATION AND P WAVE IN LEAD II*

| No. of Dog | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Duration of $P_2$ | 0.060 | 0.050 | 0.065 | 0.055 | 0.045 | 0.055 | 0.040 | 0.050 | 0.045 | 0.055 | 0.040 | 0.040 | 0.050 | 0.060 | 0.045 |
| Time the Sinus Head Activity Precedes the Beginning of $P_2$ | 0.015 | 0.007 | 0.005 | † 0.000 | 0.005 | 0.015 | 0.012 | 0.008 | 0.005 | 0.015 | 0.015 | 0.010 | 0.005 | † 0.000 | 0.005 |
| Segment on the Descending Limb of $P_2$ at Which the end of Auricular Activation is Referred | Sup. 1/3 | Mid. 1/3 | Inf. 1/3 | Sup. 1/3 | Inf. 1/3 | Sup. 1/3 | Inf. 1/3 | Mid. 1/3 | Inf. 1/3 | Mid. 1/3 | Mid. 1/3 | Inf. 1/3 | Mid. 1/3 | Sup. 1/3 | Inf. 1/3 |

*For this table only 15 dogs were considered.
†In these cases an initial slurring of P is present.

which we have marked the principal activation moments. In most of the cases, sinus activity takes place from 0.005 second to 0.015 second before the inscription of the P wave. However, in some instances it is difficult to see the exact beginning of P in the peripheral leads due to the presence of an initial slurring. The end of the right activation never goes beyond the apex of the P wave. When this wave is bifid, the activation always ends before the second peak. The septal activation corresponds to the inscription of the ascending segment of the P wave.

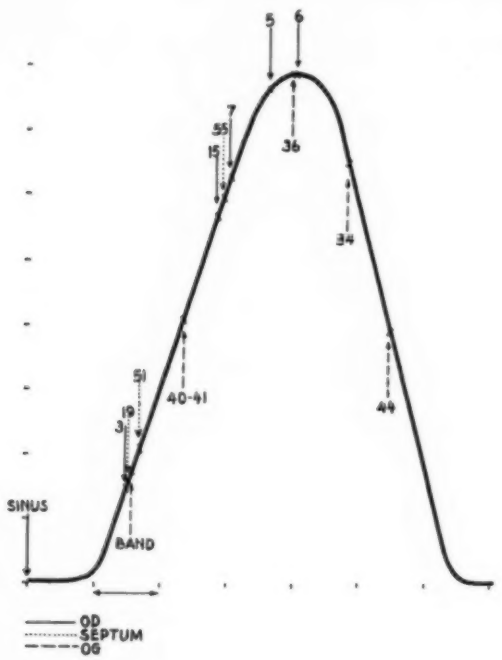


Fig. 7.—Schematic representation of the P wave in Lead II, in relation to the electrical activity of the auricles (registered at different points of the epicardial surface) and the septum (endocardial surface).

The left auricular activation encompasses most of the ascending segment of P, and the middle or lower third of the descending portion of the wave. In all experiments we have thus far been unable to correlate the final part of the P wave with the activity of any epicardial auricular point.

The auricular conduction rate was measured only at the external surface of the right auricular body and appendage because the complex auricular architecture makes difficult the measurement of the distance between the sinus node and the different points explored at the remaining regions.

Three different series of points were studied (Table IV), first along the Taenia terminalis, second at the middle zone of the auricular body, and third along a line traced from the sinus node to the tip of the right appendage. The measurements

obtained indicate that there is a marked difference between the conduction speed along the Taenia terminalis and the remaining right auricular regions. The values obtained for the intercaval region range from 950 to 1,300 mm./second. However, in some instances very high values were registered (up to 4,000 mm./second) between the head and the middle portion of the sinus node (from point *1* to point *2*). The conduction rate for the remaining portions of the right auricular tissue ranges from 487 to 1,300 mm./second. It was found in most of the cases that the values are under 1,000 mm./second. The conduction speed was found to vary from one dog to another; however, in the same animal the values were

TABLE IV. CONDUCTION RATE VALUES WHICH HAVE BEEN REFERRED TO INITIAL ACTIVITY OF THE SINUS NODE

| NO. OF DOG | TAENIA TERMINALIS | EXTERNAL ASPECT OF RIGHT AURICULAR APPENDAGE | EXTERNAL ASPECT OF RIGHT AURICLE |
|---|---|---|---|
| 1 | 1–2:1,200 | 1–9:400 | 1–15:570 |
| 2 | | 1–7:823 | 1–15:1,100<br>1–17:1,000 |
| 3 | 1–2:1,100<br>1–3:1,300<br>1–4:1,250 | 1–9:715<br>1–10:840<br>1–7:930 | |
| 4 | 1–2:1,200<br>1–3:1,000 | 1–8:800 | 1–13:550<br>1–16:525<br>1–17:515 |
| 5 | 1–4:1,050 | 1–6:1,000<br>1–9:487 | 1–15:765 |
| 6 | 1–4:1,320 | 1–9:920 | 1–15:700 |
| 7 | 1–2:4,000<br>1–4:1,500 | 1–5:1,100<br>1–9:720 | 1–15:1,100 |
| 8 | 1–2:950<br>1–3:950<br>1–4:800 | 1–9:540<br>1–8:550<br>1–6:750 | |
| 9 | 1–2:4,000 | 1–5:1,200<br>1–8:920 | |
| 10 | | 1–10:1,100<br>1–8:765 | 1–17:760 |
| 11 | 1–2:1,400 | 1–8:600 | 1–17:580<br>1–15:715 |
| 12 | 1–2:3,000<br>1–3:2,900 | 1–7:1,370 | 1–15:1,900 |
| 13 | | 1–9:1,000<br>1–11:875 | 1–18:860<br>1–15:1,000 |

Two first figures represent the chosen points on the epicardial surface for measuring the conduction rate. The third figure corresponds to the speed values in mm./sec.

For this table only 13 dogs were considered.

always higher in the region of the Taenia terminalis, but the speed at which the impulse travels on the right auricular body and appendage is virtually the same in all experiments.

## DISCUSSION

The origin of the electrical impulse has been found to be located at the head of the sinus node. Our experiments confirm entirely the findings of Wybauw,[4] Lewis and associates[5,7,8], and Eyster and Meek[6,9,10]. It is on the epicardial projection of the sinus node head where the earliest pure negative deflection is recorded. We believe that the electrical recording is still the best way of knowing the origin of the heart impulses. In the sinus node itself, it is possible to find deflections of different morphologies and activation times. Our electrical findings concerning the origin of the impulses do not agree with the conclusions of Prinzmetal and associates[20], which were based upon cinematographic observations. These authors found that the origin of the auricular contractions is located at the midpoint of the Taenia terminalis, which corresponds to the middle or inferior part of the sinus node. We explain this apparent discrepancy between mechanical and electrical events by the rapidity with which the electrical activation travels within the sinus node.

The complex activation process of the auricles is explained by their general architecture, which is not as simple as considering them two hemispheres separated by the septal plane. However, it is generally accepted that the parietal thickness is practically negligible and that the electrical impulses travel simutaneously on the epicardial and endocardial surfaces. Thus, we may simplify the architectural understanding by taking the whole structure as bidimensional instead of tridimensional as in the case of the ventricles.

The problem concerning the possible existence of specific ways of conduction is still unsolved. Our findings show that there are two regions (the intercaval and the interauricular band zone) where the impulse appears to travel with extreme ease. The septal activation at the region of the auriculoventricular node takes place at times varying from 0.025 to 0.030 second. This activation time could be very well compatible with a muscular speed, without the intervention of sino-nodal specific paths.

The activation values obtained by Lewis and associates[7] are similar to ours notwithstanding the different methods employed (Table II). We have expanded upon Lewis' electrical exploration by registering the activation process of the anterior and posterior auricular aspects, the entire septum, and the region of the pulmonary veins entrance. It is in the region of the inferior left pulmonary vein where the impulse ends and not at the tip of the left auricular appendage as was generally accepted.

In accord with the dipole theory, there is a close relationship between the morphology of the complex obtained and the activation time at a given point.[22,23] The regions near the point of origin of the activation wave show a purely negative or predominantly negative morphology; at midway of the origin and end of the impulse the morphology is diphasic; at the region last activated the morphology is predominantly or entirely positive. In general, the above concept may be applied to atrial activation. However, there are places where the activation

time and morphology do not keep such relationship, as for instance in points *4*, *14* and *29* where the activation takes place almost simultaneously and the morphology of the complexes is: rS, RS and Rs, respectively. The opposite also occurs. There are points with nearly similar morphology (rS complex), and different activation times, for example, points *1*, *25* and *38* which are activated at 0.015 second, 0.0262 second, and 0.0350 second, respectively. These findings prove that the auricular activation, as a global phenomenon, influences the morphology of the epicardial tracings. The morphology of each lead depends not only on the activation moment of the explored point but on the orientation of all the instantaneous vectors in the auricles. These are responsible for the pre- and post-intrinsic phenomenon. The intrinsic line is determined by the sudden potential variations at the arrival of the activation wave to the point explored.

## CONSIDERATIONS ON ABNORMAL AURICULAR ACTIVATION

The auricular activation has been only studied in certain conditions as flutter and auricular fibrillation.

In the dog's heart using distant bipolar leads, Rosenblueth and Garcia-Ramos,[24,25] were able to demonstrate in the experimentally produced auricular flutter that the activation wave follows a "circus movement" around an obstacle formed by the insertion of both venae cavae and an injured area uniting the two orifices. The only objection to Rosenblueth's work is that they used distant bipolar leads by which it is difficult to distinguish the intrinsic phenomenon from the extrinsic one. Nevertheless, the record of Rosenblueth strongly suggests, in those particular experimental conditions, the existence of the so-called "circus movement" mechanism.

Very recently Prinzmetal and associates[20] have proved that tracings usually interpreted as auricular flutter are not due to the "circus movement" mechanism but to an auricular paroxysmal tachycardia. These authors (personal communication) have obtained epicardial unipolar tracings directly from the auricles, in human beings with flutter or auricular fibrillation in whom mitral comissurotomy was performed. These records suggest that auricular fibrillation or flutter are actually a paroxysmal auricular tachycardia and do not correspond to the "circus movement" mechanism.

Cabrera and Sodi-Pallares[26] have studied a typical case of auricular flutter. Using esophageal and anterior chest leads they were able to demonstrate the existence of "circus movement" mechanism. The intrinsicoid deflection in the flutter waves of each one of the leads was referred to a control lead. They proved that whereas the anterior aspect of the auricular mass was activated from above downward, the posterior aspect was activated reversely.

As we have already seen, the complex auricular architecture determines the irregularity of the wave fronts, especially of those of the posterior aspect of both auricles. This is the reason why some sites near the sinus node are activated later than other areas distant from it. For instance, point *40* is activated after point *47* although this latter is at a greater distance from the sinus node. This, obviously, could mislead one to think that the activation wave travels from below upward.

More experimental work will be required before any categorical statement is made. At present, however, it looks as if the "circus movement" mechanism exists under certain experimental conditions. On the other hand, it seems also that the majority of cases diagnosed as auricular flutter by standard leads do not correspond to the "circus movement" but they are, actually, cases of auricular tachycardia. In few cases a "circus movement" mechanism may exist.

It is even more difficult to determine the mechanism of auricular fibrillation, and there seems to be no adequate explanation with a firm experimental basis.

## SUMMARY AND CONCLUSIONS

1. The auricular activation study has been simplified by means of a new technique for exposing those regions of the auricles which are difficult of approach (anterior and posterior aspects and the interatrial septum) and with the use of special unipolar and bipolar electrodes.

2. The systematic exploration of numerous epicardial and septal points has permitted the analysis of the morphology of the complexes found in each particular point. It was possible to draw the topographic distribution of the activation current on the auricular surface and septal region in reference to time. No close parallelism was found to exist between the morphology obtained in a given point and the activation time.

3. The posteroinferior region of the left auricle, near the entrance of the inferior pulmonary veins, was found to be the last zone of activation. This finding is in disagreement with the classic concept that considers the tip of the left auricular appendage to be the last activated region.

4. The septal auricular activation occurs from above downward, and from back forward.

5. In the regions of the epicardial projection of the sinus node, and over the interauricular band, the electrical impulse travels most rapidly.

6. The conduction rate of the right atrial body and its appendage ranges from 487 to 1,100 mm./second.

7. The simultaneous recording of the activity of different auricular epicardial points and Lead II permitted the schematic representation of the auricular activation in reference to the P wave.

8. Further experimental work is required to explain more satisfactorily the mechanism of auricular flutter and fibrillation.

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# SPREAD OF ACTIVATION IN THE LEFT VENTRICULAR WALL OF THE DOG. II.

## Activation Conditions at the Epicardial Surface

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### INTRODUCTION

THE order in which these papers are presented is based, with a few exceptions, on the development of the investigation as carried out in the last few years.

The epicardial curves obtained by the use of a high fidelity instrument showed numerous peculiarities, especially in the shape of the intrinsic deflection. To establish the relation between surface activation and the intrinsic deflection, differential electrodes were used.

The necessity for an investigation of the intramural activation conditions was made more urgent by the controversy which still exists on the subject of the intramural extension of the Purkinje system. It was, for instance, by no means certain whether the activation of the myocardium gave rise to a self-propagating activation front. The method of Wilson and associates[1] for transmural leads seemed to offer a possibility of closer approach to this problem.

What is registered, however, is only a summation of all processes occurring between the transmural electrodes, and it therefore appeared desirable to explore the layers of the wall itself.

Experiments with a single intramural electrode gave curves which could not be explained without further analysis. The most important tool in this investigation was the 8-electrode needle already described.[2] Use of this needle indicated that a more or less synchronous activity occurs in the innermost layers and that in the outermost layers it is possible to speak of a regularly propagated front. Between these two regions a layer was found in which irregular complexes, often leading to the so-called reversal phenomenon, were picked up. These findings led us to extend the investigation in three directions:

(a) Investigation of the angle which the more or less regular activation front in the outer layers of the wall makes with the epicardial surface. For this purpose several 8-electrode needles had to be introduced into the heart at the same time.

(b) Study of the properties of the longitudinal propagation in the inner layers, which also required the insertion of several 8-electrode needles into the wall.

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Received for publication Aug. 28, 1953.

(c) Study of the behavior with respect to extrasystoles induced from the epicardial or the endocardial side. This was done by using two adjacent lead points of the compound electrode needle as stimulating electrodes.

All these investigations considered together finally gave us the picture that we propose to describe in a series of papers. This paper deals with the surface registrations.

## INVESTIGATION OF ACTIVATION CONDITIONS AT THE EPICARDIAL SURFACE OF THE LEFT VENTRICLE

In the investigations, described in this paper, use was frequently made of a surface electrode with a small contact area which permits leading off from very small regions of the heart. This surface electrode consists of a piece of cotton-wool soaked in isotonic saline and drawn out to a fine point. The reference electrode was always placed in the subcutaneous tissue of the left hind leg. The action curves registered in this way showed numerous details which are not brought out when the usual apparatus is employed. In the QRS complexes there are sometimes small irregularities or even notches. The well-known smooth course of the QRS complex must be ascribed in a large measure to the type of apparatus commonly used.

At certain places on the surface of the ventricle the first part of the R wave rises rather slowly above the zero line and does not assume its steeply rising aspect until later.

Peculiarities in the form of the intrinsic deflection are of interest. The term intrinsic deflection is here used in the conventional sense, but our ideas on this matter will appear from what follows. This deflection is more complex than has so far been assumed. In the complexes which can be registered from most parts of the ventricular surface, the intrinsic deflection is found to consist of three parts: a first slow portion follows directly after the peak of the R wave and a second slow part comes before the nadir of the S wave. Between these two a very fast portion is found. This fast portion seldom shows irregularities. The S wave is often slightly irregular in shape, as is also the R wave. In the cases where a Q wave could be demonstrated, this was found to be not quite regular either. In that part of the left ventricle where the muscular wall is thick, the last, slow portion of the intrinsic deflection was absent and the QRS complex ended with a somewhat faster portion. At a few places on the left ventricle we found no fast portion at all. The same was observed in leads from places of early activation on the right ventricular surface.

### *Experiments With Surface Differential Electrodes.*

An epicardial lead and a differential electrocardiogram over a small part of the surface were taken simultaneously. The epicardial lead was taken between one of the lead-points of these surface differential electrodes and the left hind limb. In the majority of cases the differential electrocardiograms show a remarkably fast deflection lasting no more than 3 milliseconds. These complexes are seen only

with a favorable placing of the electrodes. Often we found these fast deflections (spikes) only after cautiously turning the electrodes. In some cases even with a very thorough search it was impossible to elicit fast deflections from a certain part of the surface. Smaller, slightly irregular deflections were often seen before and after the spike. The portion of the surface under examination is activated at the moment that the maximum of the spike is reached. Because of the movements of the heart it was not always possible to continue leading off from one spot for any length of time, as small displacements occurred. Remarkably large changes in the form of the differential electrocardiogram were seen as a result of these small displacements of the differential electrode. There was sometimes even a change of sign.

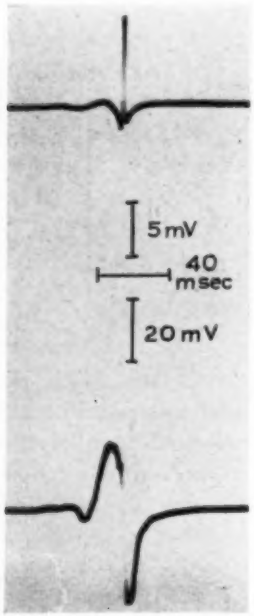


Fig. 1.

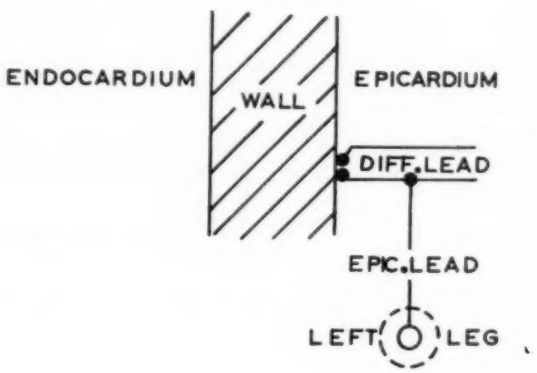


Fig. 2.

Fig. 1.—Differential epicardial lead synchronous with the first portion of the intrinsic deflection. The lower curve is recorded with normal epicardial lead. Method of registration is shown in Fig. 2.

Fig. 2.—Scheme of leads normally used for the investigation of surface phenomena.

In a few cases the differential complex consisted of several fast deflections, sometimes even of opposite sign. This indicates that, despite the smallness of the area led off, several small activation waves are occurring in the region under examination, and that these are being registered or at any rate are influencing the differential electrocardiogram. In the epicardial leads these phenomena are, of course, not observed. These multiphase components were found only occasionally. Leads from a thickened part of the epicardium confirmed our views that the fast part of the differential electrocardiogram originates from electrical

processes directly under the electrode. Even where the epicardium was thickened only slightly, the fast complex could no longer be found.

To ascertain at what time during the unipolar epicardial complex the corresponding subepicardial muscular tissue becomes activated, a differential electro-

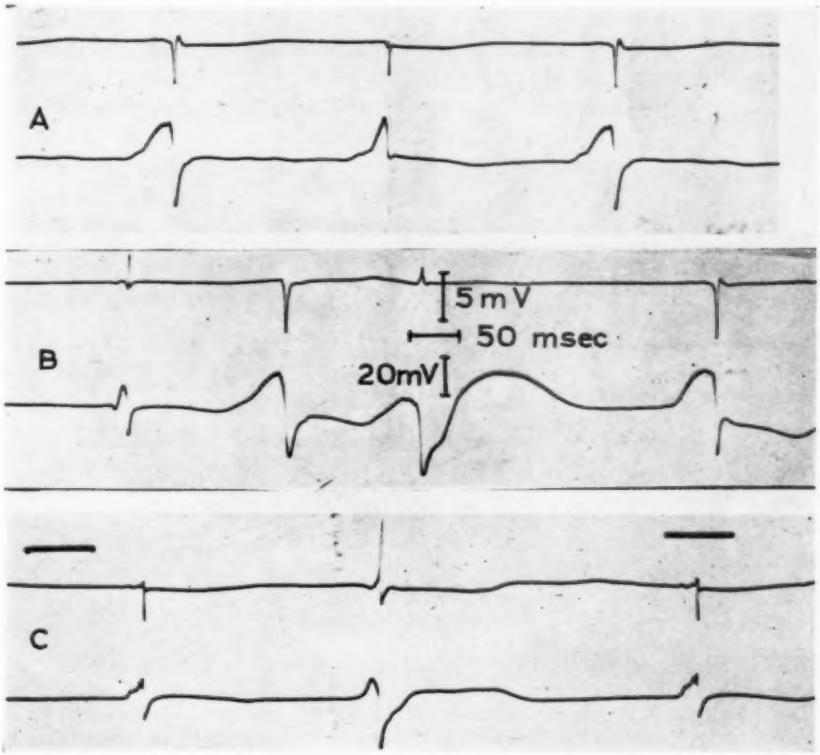


Fig. 3.—A, B, C. Upper curves: differential leads. Lower curves: epicardial leads. Extrasystoles were elicited by mechanical stimulation. The second complex in *A*, the first one in *B*, and the first and third complexes in *C*, are normal beats. In all complexes the spike coincides with the fast portion of the intrinsic deflection. Curve *C* is particularly interesting. Here the normal differential spikes are equal. The extrasystole gives rise to a differential spike of reversed polarity.

cardiogram and a subepicardial electrocardiogram were registered together. In all cases where a fast part of the intrinsic deflection could be detected, the top of the differential spike was found to coincide with it. This shows that the surface becomes activated at the moment that the fast part of the intrinsic deflection is registered. Where no fast part of the intrinsic deflection could be demonstrated, the top of the differential electrocardiogram always coincided with a part of the intrinsic deflection.

In some experiments extrasystoles were evoked by mechanical stimulation. With stimulation in the immediate neighborhood of the exploring differential electrode there appeared QS complexes in which no intrinsic deflection was dis-

cernible. Here the top of the differential electrocardiogram always corresponded to the first part of the descending limb of the QS complex. But when the other ventricle was stimulated there appeared wide positive complexes with an obvious 3-stage intrinsic deflection. The maximum of the differential electrocardiogram then also coincided with the fast part of the intrinsic deflection in all instances.

The fact that the shape of the differential electrocardiogram during extrasystoles differs from that during normal beats, for a certain position of the electrode, might suggest the possibility that small displacements of the differential electrode are caused by the extrasystoles. As already remarked, such small displacements greatly influence the shape of the differential electrocardiogram, whereas the

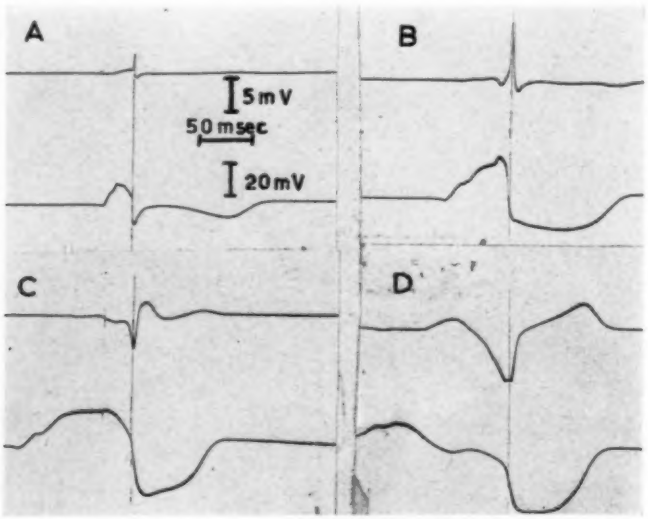


Fig. 4.—Increasing anoxemia was induced by stopping the respiration pump. The upper curves of Fig. 4 show the differential lead from a certain part of the surface and the lower curves the corresponding epicardial lead. In the electrocardiogram taken before the pump was stopped (Fig. 4, B) there appeared a progressive broadening of the QRS complex and of the differential electrocardiogram, but the top of the differential spike still coincided with the fast part of the intrinsic deflection. As the anoxemia increased (Fig. 4, C, D), the epicardial and differential complexes broadened still more, but the time relationship between the top of the spike and the intrinsic deflection was maintained. This very marked broadening of the complexes indicates an extremely low speed of conduction of the activation process.

epicardial leads are only slightly affected. This is explained by the fact that the differential electrocardiogram registers only the electrical events taking place immediately under the electrode, whereas the normal epicardial leads give information concerning a much larger region. Another possibility is that the activation process of these subepicardial muscle tissues in normal beats runs a course different from that in extrasystoles, even when these are induced by stimulation of a point of the right ventricle.

Figure 3, C shows that in both the differential and epicardial electrocardiograms the shape of the complex after the extrasystole was the same as that before it. It is therefore probable that the different shape of the differential

complex during this extrasystole indicates a different epicardial course of the impulse. In other experiments of this kind the change in the differential electrocardiogram was probably due to displacement as the differential electrocardiogram after the extrasystole was not the same as that before it.

The relationship between the top of the differential spike and the intrinsic deflection of the unipolar curve registered at the epicardium is also maintained under pathological conditions. The following experiment gives an example of this:

Increasing anoxemia was induced by stopping the respiration pump. The upper curves of Fig. 4 show the differential lead from a certain part of the surface and the lower curves the corresponding epicardial lead. In the electrocardiogram taken before the pump was stopped (Fig. 4, A) the maximum of the spike coincides with the clearly visible fast part of the intrinsic deflection. A few minutes after the pump had been stopped (Fig. 4, B) there appeared a progressive broadening of the QRS complex and of the differential electrocardiogram. But the top of the differential spike still coincided with the fast part of the intrinsic deflection.

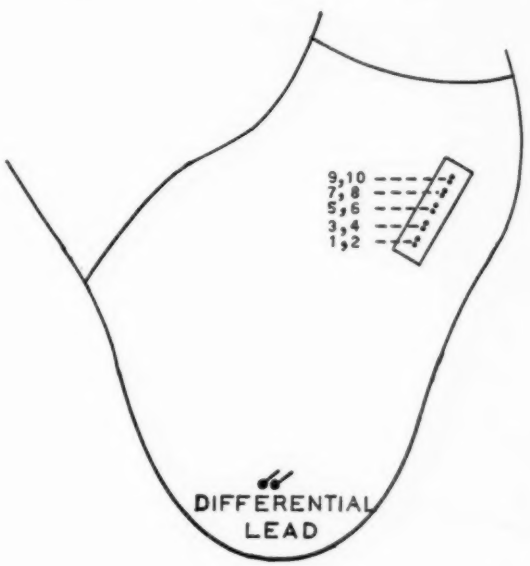


Fig. 5.—Scheme of use of multiple differential leads.

As the anoxemia increased (Fig. 4, C and D) the epicardial and differential complexes broadened still more, but the time relationship between the top of the spike and the intrinsic deflection was maintained. This very marked broadening of the complexes indicates an extremely low speed of conduction of the activation process. That the differential lead still gives recordings with a high voltage can only be caused by the fact that the geometrical properties of the activation front have not changed much. The distance between source and sink is not much increased. Compare our remarks about differentiation in space and in time in our preceding paper.[2]

The occurrence of large, fast differential deflections in normal beats indicates that the activation of the outer layer takes place in such a way that important fast components spreading over the surface are always present. The fact that it is sometimes necessary to turn the differential electrode in order to get a large fast deflection is explained as follows:

A large, fast deflection is obtained when the line connecting the differential electrodes lies parallel to the direction of propagation. If the connecting line is parallel to the wave front (perpendicular to the direction of propagation) the

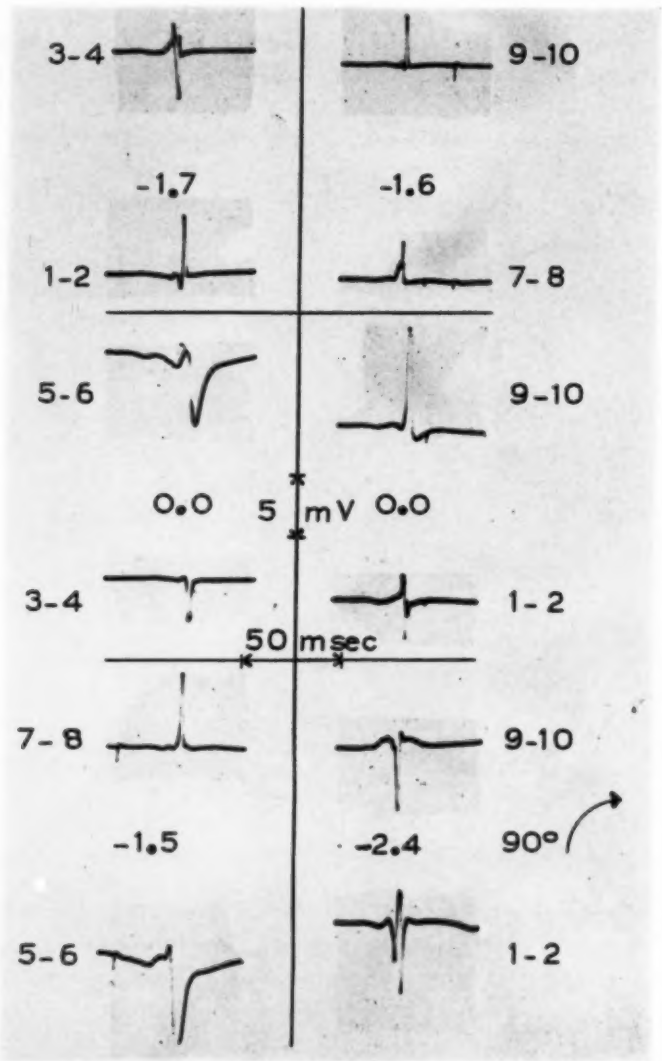


Fig. 6.—Recording with a 5-differential surface electrode in the apical region. 1-2, 3-4, etc., are differential leads; compare Fig. 5. The differential spikes all occur in very small time intervals which are given in milliseconds between each two curves of a registration. Method of registration, also for Fig. 6, is shown in Fig. 7. The inaccuracy in the time is ± 0.5 msec. owing to the already mentioned variability of surface registrations with the place.

front reaches both electrodes at the same moment and all components decrease in amplitude. In view of the marked variations in shape and direction of the differential deflections with small displacements of the differential electrode, it is necessary to assume that in adjacent small regions of the ventricular surface the directions of the activation impulse must sometimes be opposite. To investigate this point, a larger region of the surface of the ventricle was explored with the 5-differential electrode previously mentioned.[2] The construction of this electrode ensures a constant spacing of the differential lead points.

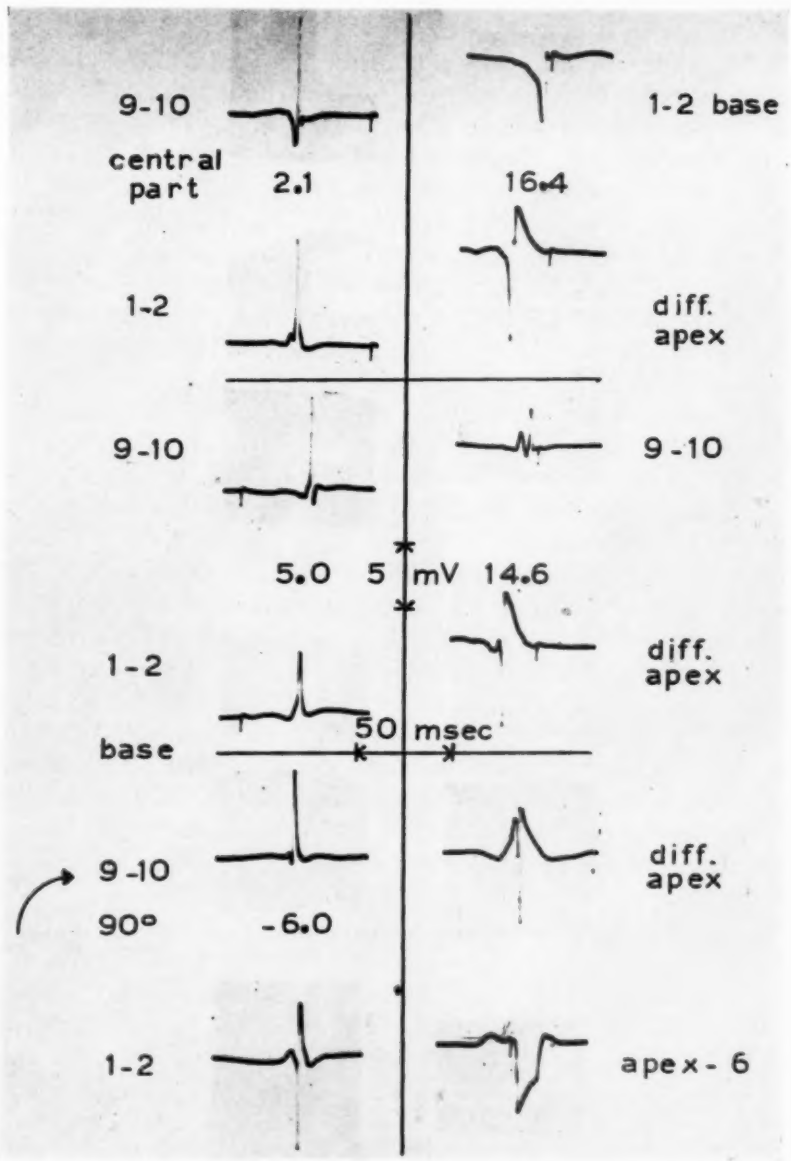


Fig. 7.—Like Fig. 6 for middle and basal parts, also recordings from longer distances are given.

In leads from the apical region (Fig. 6) the spikes in all leads of the row are separated by very small time intervals (max.=3 milliseconds). The polarity of these spikes was different from that which would be expected from an activation front with regular propagation. From this varying polarity it must be concluded that multiple activation waves are propagated for a short distance in several directions under the surface electrode. When the electrode is turned through 90° the time interval in the apex region still remains small, and it is also impossible to detect a regularly propagated activation front in this way. In the middle part of the left ventricle (Fig. 7) essentially similar phenomena are found, although the interval between the spikes is somewhat larger. The range over the various differential leads is here up to 6 milliseconds. In the basal part of the left ventricle also, no activation process advancing regularly along the surface could be demonstrated. The activation conditions at the surface as examined in this way are made somewhat clearer if one differential electrode is placed in the apical and the other in the basal region. It is then found that the apical region is activated earlier than the basal region, the interval being about 15-30 milliseconds approximately.

In all observations it was demonstrable that the basal region was activated later than the apical. Roughly speaking we may thus conclude that an activation front advances in an apico-basal direction over the surface of the left ventricle.[3]

Attempts to determine the speed of propagation of the activation process by measurements at the surface give values of several meters per second. Despite the fact that the measurement of time intervals between two differential electrodes, one at the apex and one at the base, reduces to a minimum the chance of error due to small deviations in the intermediate region, the values found in this way for the velocity of propagation are too high. There must, therefore, be other sources of error in this method.

The velocity of propagation is usually calculated by dividing a distance by an observed time interval. But, as will be shown in a subsequent paper, the angle between the activation front in the outer layers and the epicardium is small. This means that a small bulge or irregularity in the front will in a certain region reach the epicardial surface first. At the epicardial surface it will then seem as though the activation wave spreads from that point over a certain region. The activation front is in fact irregular in shape, so that the above mentioned phenomenon appears at many points on the epicardial surface. Only if the front were perfectly "smooth" and spread as a sharply defined phenomenon under the epicardial surface, would it be possible to determine the velocity of propagation by measurements at the surface.

In 1935 Wilson and associates[1] calculated the potential variations that an electrode will undergo when an activation front approaches and passes it. They described the electrical field produced by activation of the muscle layer as a dipole area. They showed that the approach of the dipole front gives rise to a positive deflection and its passage to a fast deflection in the other direction which may extend far below the zero line as the front moves away from the electrode, to come back to the zero line afterwards. This rapid deflection was called intrinsic deflection by Lewis.[4] The speed of the deflection is due to the fact that the angle subtended by the dipole front at the electrode changes rapidly in magnitude and

sign. The shape of the definite curve is determined by the geometrical conditions, including the angle made by the dipole front with the direction of propagation.

Wilson and associates were able to demonstrate a remarkable correspondence between the mathematical formula based on the given assumption and the curve actually registered from the surface of the auricle.

According to Lewis, who was the first to draw attention to the great importance of the intrinsic deflection, the maximum of this large and rapid deflection arises from activation of the muscle tissue lying directly under the epicardial electrode. He was of the opinion that the subsequent negativity of the deflection was due to the fact that the muscle tissue which had become negative under the influence of the activation exerted a strong negative effect on the electrode situated over it. He did not attempt to give direct experimental proof of this. In recent years several investigators have studied this phenomenon. Harris[5] demonstrated, with the aid of two electrodes placed close together (a kind of differential electrode with a relatively large distance between the lead points), that the moment of activation coincided with a point in the intrinsic deflection. He was of the opinion that activation occurred at the beginning of the largest deflection in the "differential" electrocardiogram. Although this is not quite correct, since the peak of the deflection actually indicates the moment at which the activation wave reaches the first lead point, the time intervals in question are so small that this assumption may be considered reasonable, especially for the rather slowly reacting apparatus with which Harris worked. Sodi-Pallares and associates used a somewhat modified method. They found that the moment of activation coincided with a point in the lower part of the intrinsic deflection.

Schaefer[7] showed that a fast part was detectable in the intrinsic deflection. He believed that this fast portion occurred during the activation of the surface, but he did not offer any experimental evidence for this view.

The concept "moment of activation" is of course an abstraction. In reality there is always a finite time interval in which the activation, even of isolated muscle fibers occurs. With our method of investigation this time interval is partly dependent on the size of the area lead off. Even if, as has been demonstrated, several activation waves occur in a small area we believe the range to be so small that one may speak of the activation moment.

It is very important that the electrical processes which occur as a result of activation of muscle tissue lying immediately under the electrode can be traced in a given epicardial lead. They are represented by the rapid part of the intrinsic deflection. We can now apply the term "intrinsic" only to this fast part. The slower parts which precede and follow this, if present, can no longer be called intrinsic, but they have to be considered together with the peaks as part of the extrinsic deflection.

A fast portion in the curve registered occurs only when the dipole area passes within a short distance of the exploring electrode. If this electrode is not placed on the heart muscle directly but at some distance from it, the spatial angle subtended by the dipole area will not show any great discontinuity. If the electrode is situated at a distance comparable with the thickness of the heart wall, we can

expect a curve in which the descending limb is not very much steeper than the ascending one. For a lead at a distance the concept of intrinsic deflection loses its meaning. By many authors this deflection is called intrinsicoid.

With such a precordial lead it is necessary to take into account the fact that the electrical relations between various points on the wall and the exploring electrodes differ greatly.

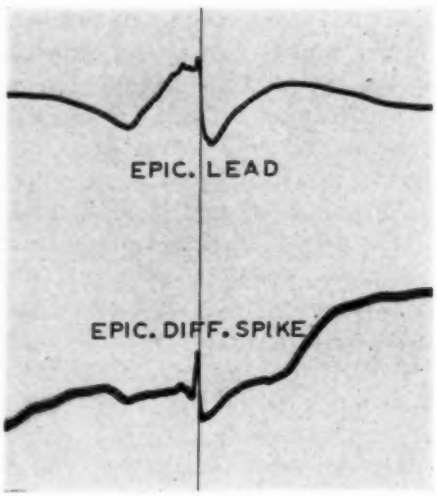


Fig. 8.—Epicardial lead and differential spike in the exposed human heart. Because of circumstances during the operation no calibrations could be made.

In one case it was possible to demonstrate in the exposed human heart the same relationship between differential spikes and intrinsic deflections as in the dog (Fig. 8).

## SUMMARY

Registration of unipolar epicardial leads of the exposed heart of the dog with a high fidelity oscillograph reveal several peculiarities in the form of the QRS complex. For most parts of the epicardial surface of the left ventricle, the intrinsic deflection consists of three parts; a slow portion after the zenith of the R wave, one near the nadir of the S wave, and between these two parts a fast portion.

With differential leads it is proved that at the moment this part of the intrinsic deflection is written, the subepicardial muscle under the exploring electrode is activated. The differential spike coincides with the rapid part of the intrinsic deflection. In one instance this relation could be proved for the exposed human heart.

This connection holds also for extrasystoles and for the gradually widening complexes during increasing anoxemia.

By the use of multiple differential electrodes, results were obtained pointing to the existence on the epicardial surface of many activation waves propagated in a very small area.

In accord with other authors it was found that the over-all direction of the activation is from apex to base.

The concept of the intrinsic deflection was critically analyzed. Only the rapid part of the intrinsic deflection in curves obtained from the exposed heart can be called intrinsic.

In precordial leads it is impossible to find a constant point in the "intrinsic deflection" that signals the arrival of the activation wave at the epicardial surface nearest the exploring electrode.

Our sincere thanks are due to Prof. I. Boerema, M.D., and J. Glazenburg, M.D., for their kind cooperation in this experiment.

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# DURATION OF THE Q-T INTERVAL DURING THE ANOXEMIA TEST

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AS a means of detecting coronary insufficiency, Levy and his associates in 1939 proposed electrocardiographic criteria for the differentiation of normal from abnormal responses to the breathing of 10 per cent oxygen and 90 per cent nitrogen for a period of twenty minutes.[1,2,3] The changes quantitated were related only to the RS-T segment and T wave. Wide clinical experience has confirmed the objective value of this test in the diagnosis of arteriosclerotic heart disease with angina pectoris.[2-8] Yet it is also common experience to find patients with true angina pectoris who do not respond abnormally by the above criteria. The percentage of cases of true angina pectoris failing to exhibit a positive Levy test has been variously estimated to range from 45 to 70 per cent[2-5] while false positives occur in 1 to 3 per cent of the cases.[4-6]

The Q-T interval, often referred to as electrical systole, has been studied increasingly in recent years. It appears established that the measured Q-T interval, when adjusted for heart rate,* is prolonged in the following states: acute myocardial infarction,[8-10] arteriosclerotic heart disease,[10-12] cardiac failure,[13,14] cardiac hypertrophy,[14] hypertensive cardiovascular disease,[15] acute pulmonary embolism,[9,10] old age,[16] semistarvation,[17] myxedema[9] rheumatic carditis,[18-24] diphtheritic myocarditis,[9,24] acute nonrheumatic myocarditis of adults,[25] hypopotassemia,[10,26-28] hypocalcemia,[9,10,24,28-31] during quinidine[32] and emetine[33] therapy, and upon assuming the upright position.[34,35]

In a recent classification of major causes of Q-T prolongation, Bellet and Finkelstein[10] recognized anoxia as the common factor in the following varied conditions: myocardial infarction, arteriosclerotic heart disease, pulmonary embolism, recovery from Stokes-Adams attacks, illuminating gas poisoning, and the dying heart. Of Q-T prolongation, Ashman[36] writes: "It is my belief that this sign is very helpful in cases of suspected rheumatic myocarditis or myocardial ischemia." Moderate asphyxia in dogs is regularly accompanied by prolongation of Q-T. From this and comparative Q-T studies in various

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Received for publication Sept. 15, 1953.

*The subscript c is used to indicate that the measured Q-T value has been corrected for rate by the Bazett formula using the notation system of Taran and Szilagyi[18]: $Q\text{-}T_c$ = measured Q-T/$\sqrt{\text{cycle length}}$.

species, Robb and Turman[37] postulated that: " . . . Q-T duration seems to be directly related to metabolism, presumably cardiac cellular metabolism . . ." and suggest that ". . . the Q-T to cycle relationship depends on cardiac oxygen consumption . . ." White and associates[38] found that anoxemia produced by ascent to an altitude of 20,000 feet caused an increase in Q-$T_c$ of 6 per cent in seventeen normal subjects. Upon oxygen administration, Q-$T_c$ fell nearly to control values. A similar prolongation occurred when arterial oxygen saturation was reduced to 65 per cent in rebreathing experiments.

Despite the above suggestive evidence we have found no work on changes in Q-$T_c$ during the anoxemia test. The present study was undertaken to determine the effect of the anoxemia test on the Q-T interval in normal subjects and in patients with coronary artery insufficiency.

## METHODS AND MATERIAL

The effect of the Levy anoxemia test on electrical systole in forty normal volunteer subjects and ninety-five patients was investigated. Fourteen of the patients were tested a second time and three of these a third. Records were obtained and Q-$T_c$ durations determined at the beginning of the test (control), at five-minute intervals during the twenty-minute period of 10 per cent oxygen breathing and two and one-half minutes after 100 per cent oxygen breathing in all cases. All records were obtained on a 4-channel direct-writing Sanborn electrocardiograph. In twenty of the normal subjects and forty-three patients twice the conventional paper speed, 50 mm. per second, was employed. The other tests were taken at the usual 25 mm. per second. Q-T was measured in a minimum of four successive complexes to the nearest 0.005 sec. and the average obtained. The R-R interval was obtained from the average of ten successive complexes, thus eliminating variability of cycle length due to sinus arrhythmia.[39] Respiratory or nonphasic arrhythmias[40] of appreciable magnitude were not observed. During the period of anoxia the rhythm was almost always precisely regular. Lead $V_4$ was utilized for measurements in all but a few records where the presence of a U wave on the descending limb of T or an isoelectric terminal portion of T made accurate estimation difficult. In such instances another chest lead or Lead II was used. By comparison of three or four simulanetously recorded leads, it was always possible to exclude the U wave from the Q-T distance.[41,42] These same comparisons were used to avoid the error resulting from an isoelectric beginning of QRS.[42] Once a particular lead was selected for measurement, this same lead was used consistently in each tracing during the anoxemia test. Simultaneous phonocardiograms and simultaneous ballistocardiograms were recorded in many of the normal subjects and the patients. Various techniques for measurement of the "duration of mechanical systole" were explored. This data will be reported subsequently.

Measured values of Q-T were corrected for rate by the Bazett square root formula and are designated as $Q\text{-}T_c$. The calculation is easily performed with a slide rule.[42] A positive Levy test[3] is based on one or more of the following criteria:

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III and $V_4$) totals 3 mm. or more.
2. There is a partial or complete reversal of the direction of T in Lead I, accompanied by an RS-T deviation of 1 mm. or more in this lead.
3. There is complete reversal of the direction of T in Lead $V_4$, regardless of RS-T deviation.

In most of the patients precordial leads $V_2$, $V_4$, and $V_5$ were taken. In those rare instances where unequivocal T-wave reversals appeared in $V_2$ or $V_5$, the test was also considered positive. In such cases $V_4$ always showed definite changes though not of sufficient degree to be termed positive on the basis of $V_4$ alone.

The forty normal volunteer subjects (mean age 39) all exhibited negative Levy tests and are designated Group I. Forty-four patients (mean age 53) whose chest pains were judged to be of noncardiac origin form Group II. Twenty-seven patients (mean age 55) with chest pain typical of angina pectoris but who had negative Levy tests comprise Group III. Twenty-nine patients (mean age 58) with typical angina pectoris and positive anoxemia tests by the Levy criteria make up Group IV.

Classification of the patients was based upon careful evaluation of the entire clinical situation. An additional special history was obtained with close attention to relevant details. Pain of musculo-skeletal origin was the most common sort observed in Group II, with a lesser number exhibiting pleuritic type pain. In these patients, roentgenologic spine examinations, response to physiotherapy and the like served to confirm the clinical diagnosis. The patients in Groups III and IV were so classified chiefly on the basis of a definite history of typical attacks of angina pectoris coupled with such factors as coexisting hypertension, peripheral vascular symptoms, previous myocardial infarction, congestive heart failure, or syphilitic aortic disease. Among these patients, frequent rechecks of the clinical status of the individual served to confirm or deny the diagnosis. Where there was reasonable doubt as to the presence or absence of angina pectoris, the patient was excluded from the study.

Two additional patients not included in the preceding groups had positive Levy tests but were not considered to have angina pectoris or coronary artery disease (false positives). In one of these patients the diagnosis of hyperventilation syndrome was established and the other had a previous hospital course and electrocardiograms typical of acute pericarditis. No women are included in our series and no patients were receiving quinidine. Nineteen were receiving maintenance digitalis (Table I). No patient was in congestive failure at the time of the anoxemia test.

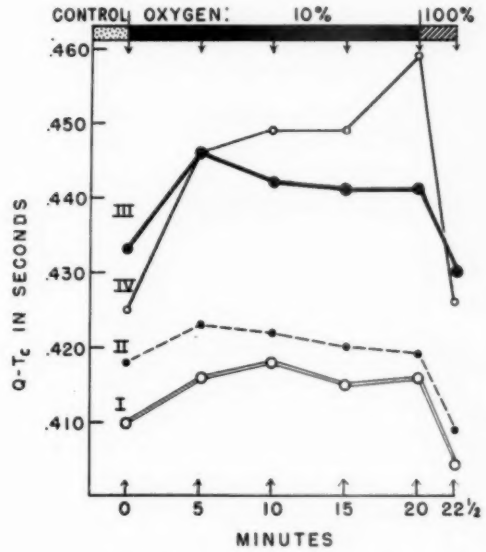


Fig. 1.—Successive mean values of Q-$T_c$ during 20 minutes of anoxia and following 2½ minutes of 100 per cent oxygen. I = normal subjects; II = patients with chest pain of noncardiac origin; III = patients with angina pectoris but negative anoxemia tests by the Levy criteria; IV = patients with angina pectoris and anoxemia tests positive by the Levy criteria.

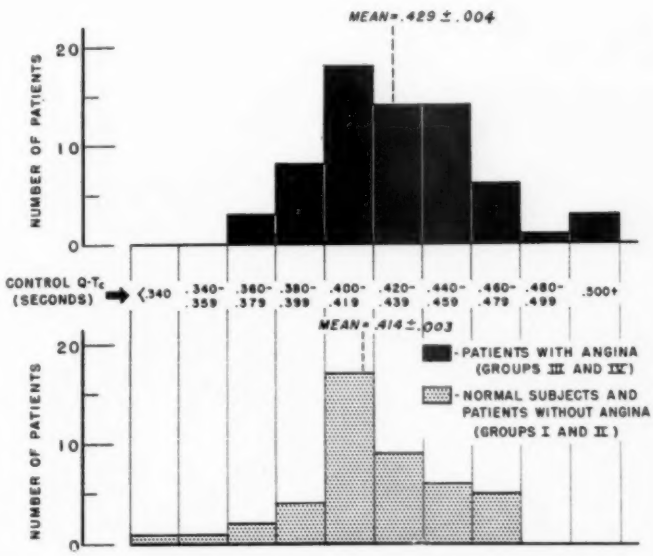


Fig. 2.—Control (initial) Q-$T_c$ values for normal subjects and all patients.

TABLE I. INITIAL Q-$T_c$, GREATEST CHANGE OF Q-$T_c$ DURING ANOXIC PERIOD, AND "Q-T ANOXEMIA INDEX" EXPRESSED IN SECONDS FOR ALL SUBJECTS AND PATIENTS

| GROUP I | | | | GROUP II | | | | GROUP III | | | | GROUP IV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SUBJECT | INITIAL Q-$T_c$ | GREATEST CHANGE DURING ANOXIA | Q-T ANOXEMIA INDEX | SUBJECT | INITIAL Q-$T_c$ | GREATEST CHANGE DURING ANOXIA | Q-T ANOXEMIA INDEX | SUBJECT | INITIAL Q-$T_c$ | GREATEST CHANGE DURING ANOXIA | Q-T ANOXEMIA INDEX | SUBJECT | INITIAL Q-$T_c$ | GREATEST CHANGE DURING ANOXIA | Q-T ANOXEMIA INDEX |
| W.H. | .390 | +.028 | .463 | J.O.D. | .443 | −.011 | .443 | B.H.* | .454 | −.014 | .454 | L.G. | .502 | +.035 | .593 |
| L.J. | .429 | +.019 | .478 | G.K. | .401 | +.017 | .445 | G.H.* | .429 | −.009 | .429 | L.Ga. | .427 | +.030 | .505 |
| G.R. | .428 | −.013 | .428 | C.D.* | .412 | +.021 | .467 | J.P.* | .402 | +.023 | .462 | A.S. | .458 | +.027 | .528 |
| J.T.R. | .410 | +.014 | .446 | F.B. | .418 | −.013 | .431 | A.T.* | .447 | +.017 | .491 | D.S. | .440 | +.026 | .508 |
| A.S. | .441 | +.010 | .467 | T.M.* | .356 | −.016 | .359 | L.B.* | .443 | +.023 | .493 | S.G. | .452 | +.034 | .540 |
| J.W. | .416 | +.012 | .447 | G.S. | .417 | −.009 | .438 | R.B. | .456 | +.018 | .503 | C.D. | .400 | +.038 | .499 |
| R.T. | .412 | +.009 | .435 | H.H. | .397 | +.040 | .501 | W.H. | .447 | +.033 | .533 | W.C. | .379 | +.055 | .522 |
| J.D. | .411 | +.017 | .455 | J.H. | .424 | −.012 | .424 | J.D. | .421 | +.024 | .483 | A.J.* | .475 | +.040 | .579 |
| J.C. | .386 | −.010 | .402 | C.C. | .423 | +.013 | .457 | W.H. | .473 | +.013 | .507 | J.H. | .417 | +.059 | .570 |
| G.T. | .413 | −.027 | .416 | J.C. | .400 | +.016 | .442 | J.V. | .426 | +.015 | .465 | W.H. | .390 | +.041 | .497 |
| T.F. | .367 | +.024 | .429 | W.R. | .377 | +.037 | .473 | K.C. | .415 | +.027 | .485 | J.G. | .457 | +.050 | .587 |
| L.A. | .413 | +.014 | .449 | J.A. | .378 | +.026 | .446 | A.C. | .439 | +.021 | .494 | R.S. | .397 | +.082 | .610 |
| J.L.C. | .401 | +.023 | .461 | P.B. | .400 | +.030 | .478 | B.T. | .388 | +.037 | .484 | R.S. | .462 | +.033 | .548 |
| H.B. | .413 | +.009 | .436 | J.G. | .416 | +.023 | .476 | O.H. | .428 | +.012 | .459 | C.L.G. | .386 | +.036 | .480 |
| E.D. | .400 | −.017 | .400 | W.D. | .423 | +.021 | .478 | A.M. | .448 | +.025 | .513 | C.L.G. | .384 | +.054 | .504 |
| H.L. | .394 | +.031 | .475 | L.A. | .397 | +.012 | .465 | A.M. | .497 | +.005 | .510 | L.H. | .394 | +.043 | .506 |
| J.B. | .442 | −.044 | .465 | L.A. | .411 | +.011 | .434 | A.M. | .504 | +.002 | .509 | L.H. | .411 | +.036 | .505 |
| R.K. | .379 | +.024 | .441 | W.G. | .472 | +.004 | .482 | E.M. | .443 | +.067 | .617 | C.Y.* | .444 | +.066 | .616 |
| L.W. | .421 | +.015 | .460 | G.L. | .421 | −.013 | .421 | F.T. | .383 | +.047 | .505 | W.R.* | .416 | +.038 | .515 |
| J.M. | .390 | +.021 | .445 | E.C. | .423 | +.018 | .470 | J.M. | .421 | +.026 | .489 | W.A. | .377 | +.055 | .520 |
| H.R.H. | .393 | +.020 | .445 | L.S. | .440 | +.014 | .476 | L.M. | .426 | +.029 | .501 | W.A. | .418 | +.038 | .517 |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| P.H. | .416 | +.022 | .473 | A.F.* | .412 | −.024 | .438 | D.B. | .411 | +.039 | .512 | C.G.* | .417 | +.051 | .550 |
| R.Y. | .370 | +.034 | .458 | B.G. | .412 | +.001 | .415 | D.B. | .388 | +.038 | .487 | J.B. | .411 | +.035 | .502 |
| L.G. | .428 | +.011 | .457 | J.R. | .416 | −.035 | .416 | T.B. | .412 | +.030 | .490 | J.B. | .440 | +.016 | .482 |
| W.S. | .400 | +.007 | .418 | A.F. | .421 | +.003 | .429 | W.O. | .425 | +.022 | .482 | J.B. | .409 | +.042 | .518 |
| W.M. | .392 | −.008 | .392 | R.M. | .421 | +.031 | .502 | C.M. | .531 | −.008 | .531 | H.R. | .424 | +.033 | .510 |
| J.M. | .405 | +.010 | .431 | W.B. | .421 | −.007 | .435 | J.B. | .411 | +.049 | .538 | J.G. | .438 | +.034 | .526 |
| M.H. | .413 | +.009 | .436 | O.D. | .440 | +.005 | .452 | P.M.* | .408 | +.033 | .494 | W.M. | .449 | +.031 | .530 |
| F.D. | .403 | +.010 | .429 | V.S. | .448 | −.016 | .448 | C.G.* | .410 | +.046 | .530 | W.M. | .462 | +.007 | .480 |
| D.R. | .444 | −.034 | .444 | P.B. | .464 | −.026 | .464 | B.R.* | .395 | +.037 | .491 | J.M.* | .408 | +.014 | .444 |
| N.B. | .438 | −.019 | .438 | F.B. | .465 | −.018 | .465 | | | | | R.G.* | .476 | +.023 | .536 |
| N.O. | .418 | +.021 | .473 | V.L. | .466 | −.011 | .466 | | | | | T.N. | .422 | +.025 | .487 |
| B.P. | .432 | −.013 | .442 | J.A. | .415 | −.017 | .415 | | | | | W.O. | .465 | +.018 | .512 |
| D.M. | .421 | +.018 | .468 | H.G. | .412 | −.022 | .412 | | | | | C.M.* | .416 | +.020 | .468 |
| H.S. | .419 | +.017 | .463 | J.W. | .462 | −.006 | .462 | | | | | J.B. | .424 | +.042 | .533 |
| C.R. | .404 | +.024 | .465 | T.S. | .454 | −.013 | .472 | | | | | P.M.* | .420 | +.038 | .519 |
| H.S. | .405 | +.026 | .473 | B.W. | .412 | +.007 | .430 | | | | | P.M. | .412 | +.056 | .558 |
| E.P. | .403 | +.018 | .450 | E.W. | .394 | +.030 | .472 | | | | | | | | |
| F.G. | .447 | +.009 | .470 | R.W. | .406 | +.026 | .474 | | | | | | | | |
| H.R. | .413 | +.009 | .429 | E.W. | .424 | −.010 | .440 | | | | | | | | |
| | | | | H.W. | .336 | +.030 | .414 | | | | | | | | |
| | | | | T.S. | .389 | +.013 | .423 | | | | | | | | |
| | | | | W.G. | .415 | +.011 | .444 | | | | | | | | |
| | | | | L.F. | .448 | +.006 | .464 | | | | | | | | |
| | | | | J.P. | .410 | +.021 | .465 | | | | | | | | |
| Mean | .410 | +.009 | .446 | Mean | .418 | +.007 | .449 | Mean | .433 | +.025 | .498 | Mean | .426 | +.038 | .524 |

*On maintenance dosage of digitalis.

RESULTS

The initial Q-$T_c$ for normal subjects (Group I) and patients with chest pain of noncardiac origin (Group II) was somewhat lower than for patients with angina pectoris whether negative (Group III) or positive (Group IV) by the Levy criteria (Table I, Fig. 1). The mean initial Q-$T_c$ for the normal subjects and patients without angina (I and II) was 0.414 ± 0.003 sec. while the mean initial Q-$T_c$ for all patients with angina whether negative or positve by the Levy criteria (Groups III and IV) was 0.429 ± 0.004 sec. (Fig. 2). Although these means are significantly different (P = < 0.01), the range of individual values is so large that

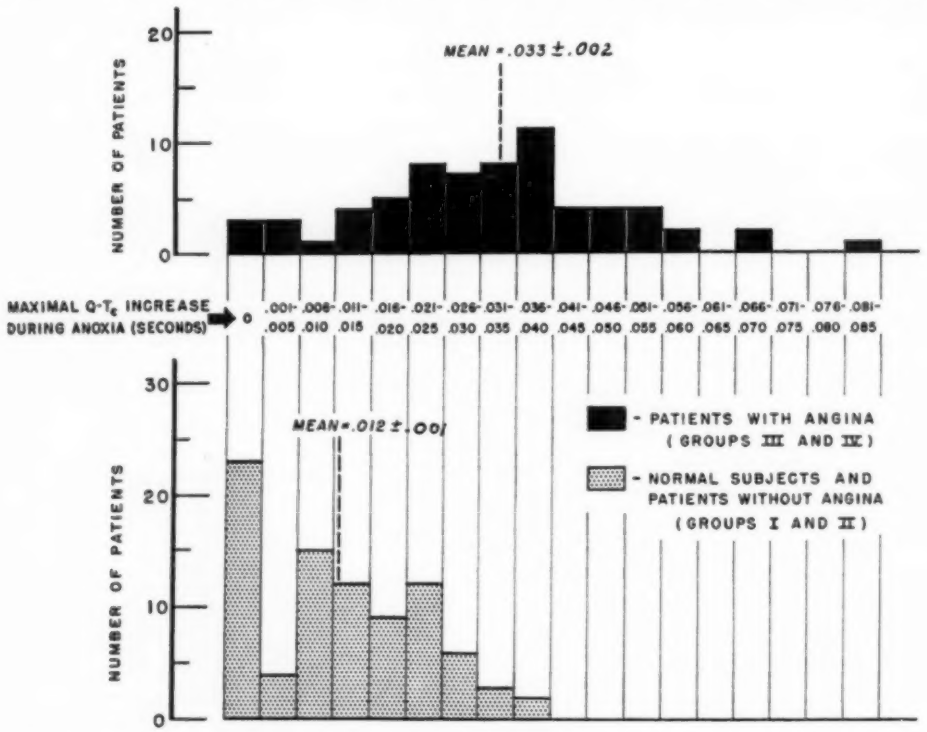
MEAN = .033 ± .002
NUMBER OF PATIENTS
20
10
0
MAXIMAL Q-Tc INCREASE DURING ANOXIA (SECONDS)
0 .001-.005 .006-.010 .011-.015 .016-.020 .021-.025 .026-.030 .031-.035 .036-.040 .041-.045 .046-.050 .051-.055 .056-.060 .061-.065 .066-.070 .071-.075 .076-.080 .081-.085
MEAN = .012 ± .001
30
20
10
0
- PATIENTS WITH ANGINA (GROUPS III AND IV)
- NORMAL SUBJECTS AND PATIENTS WITHOUT ANGINA (GROUPS I AND II)

Fig. 3.—Maximal Q-$T_c$ increase during 20 minutes of 10 per cent oxygen breathing for normal subjects and all patients. Since the abnormal response was clearly in the direction of an inordinate increase in Q-$T_c$ during anoxemia, in those tests in which the greatest change with anoxemia was a decrease in Q-$T_c$, such change is considered a zero increase in this and the subsequent figures.

a useful separation cannot be achieved. The mean of the maximal increases in Q-$T_c$ occurring during the period of low oxygen breathing for the normal subjects and patients with chest pain of noncardiac origin (Groups I and II) was lower than for the patients with angina (Groups III and IV). The normal subjects and patients without angina (Groups I and II) showed a mean of the maximal Q-$T_c$ increase of 0.012 ± 0.001 sec. as compared with a mean maximal increase of 0.033 ± 0.002 in the patients with angina (Groups III and IV, Fig. 3). These means are even more significantly different (P = < 0.001), but again the range of individual values is so great that a clinically useful separation cannot be obtained.

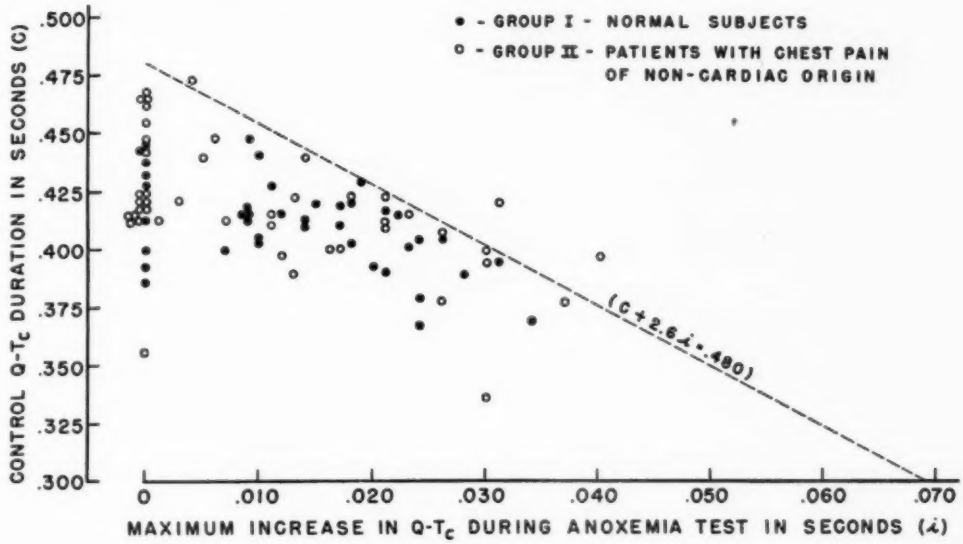


Fig. 4.—The relation of the control (initial) Q-$T_c$ duration to the maximum increase in Q-$T_c$ during the anoxemia test. Groups I and II.

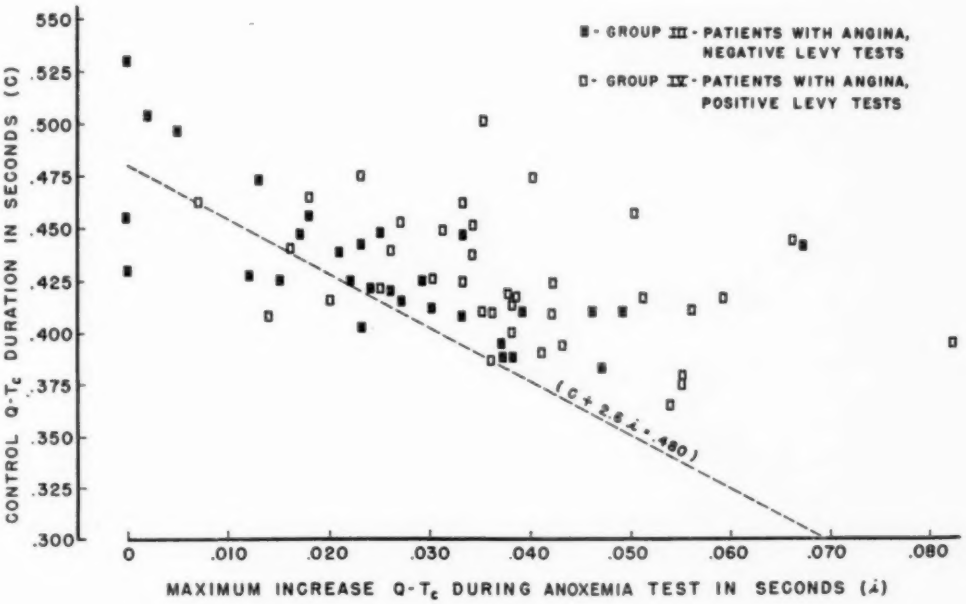


Fig. 5.—The relation of the control (initial) Q-$T_c$ duration to the maximum increase in Q-$T_c$ during the anoxemia test. Groups III and IV. The coordinates are identical with Fig. 4.

Further analysis of these data led to a consideration of the increase in Q-$T_c$ during anoxia and control Q-$T_c$ for the same patient. There was a tendency for patients with angina to exhibit a higher Q-$T_c$ control value and also to increase the Q-$T_c$ duration to a greater degree than those without angina. When the maximal increase in Q-$T_c$ during the anoxemia test is plotted on the abscissa against the control Q-$T_c$ value on the ordinate, this tendency is striking (Figs. 4 and 5). An arbitrary line can be drawn such that below this line fall all of the normal subjects and all but three of the tests on patients without angina (Fig. 4), while above this line are found 60 of the 67 tests on patients with angina (Fig. 5). This line of separation is expressed by the following equation: 0.480 sec. = (initial Q-$T_c$) + 2.6 (maximal increase in Q-$T_c$). Thus, if 2.6 times the maximal increase in Q-$T_c$ during the anoxemia test is added to the control value of Q-$T_c$, a figure is obtained which may be termed the "Q-T Anoxemia Index." The figure 0.480 appears to represent the upper limit of normal for this index with normal subjects falling below this figure and most of the patients with angina exceeding it.

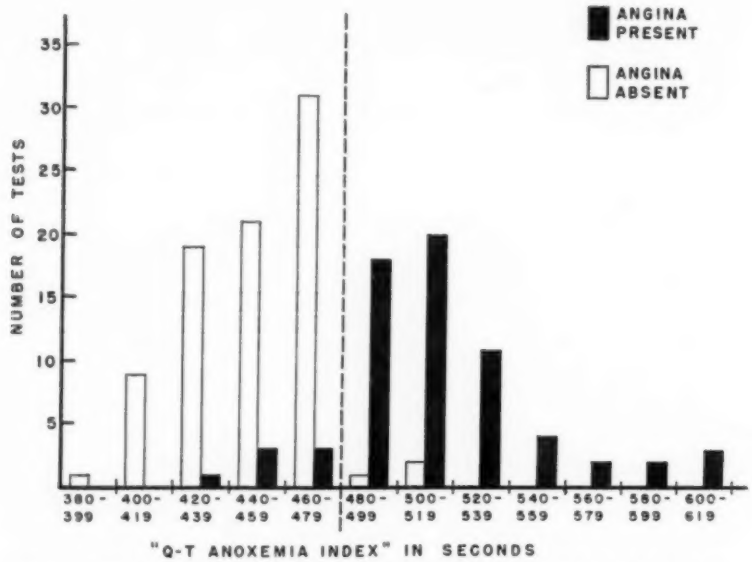


Fig. 6.—The distribution of values for the "Q-T Anoxemia Index" (see text) for all subjects and patients.

Sixty of the sixty-seven tests (89.5 per cent) in patients with angina pectoris showed a positive Q-T Anoxemia Index (Fig. 6), whereas only 37 (55.2 per cent) were positive by the Levy criteria (Table I). Of the seven patients with definite angina but a negative Q-T Anoxemia Index, five were on maintenance digitalis.

In 87 tests on subjects or patients without angina, three patients (3.4 per cent showed false-positive Q-T Anoxemia Indices. Only two of these 87 (2.3 per cent) showed false-positive tests by the Levy criteria. The first of the latter two patients was a 41-year-old Negro man with hyperventilation syndrome. During the test, the respiratory rate averaged 67 per minute, and the volume of air ventilated was 19 liters per minute. A total RS-T depression of 3 mm. was noted in the

limb leads. The T wave became partially inverted in Lead I and completely in Leads II and III. Q-$T_c$ rose from an initial 0.437 to 0.462 sec. during the period of anoxia, the Q-T Anoxemia Index being 0.502. On the following day when hyperventilation was absent, Q-$T_c$ was 0.376. The other unusual case, a 24-year-old white man, had proved pericarditis several months previously. Although he had no history of coronary artery disease, an anoxemia test was positive on the basis of complete inversion of T in $V_4$. Q-$T_c$ did not increase significantly during the test period.

## DISCUSSION

Q-$T_c$ prolongation in anoxemia was considered by White and associates[38] to occur particularly when tachycardia was present, measured Q-T failing to shorten proportionately to the R-R interval decrease. Changes in Q-T duration regularly lag behind changes in heart rate to varying extents: two to three minutes after the termination of exercise[44], and ten to thirty seconds[34] after assuming the upright position. The fact that a five-minute period of low-oxygen breathing precedes the first electrocardiogram taken during anoxemia makes it highly unlikely that this lag phenomenon is an important factor in this study, inasmuch as tachycardia appears after one or two minutes of anoxia, the heart rate leveling off well before the five-minute measurement. The five, ten, fifteen, and twenty minute electrocardiograms show remarkably little variation in rate, Group IV showing a 6 per minute increase, with even less variation in the other groups during this entire period. The precipitous fall in Q-$T_c$ after 100 per cent oxygen administration may in part be explained by the lag phenomenon[34,44] since the measurements were made after only two and one-half minutes of pure oxygen breathing. No conclusions in this study, however, are based on Q-$T_c$ changes after 100 per cent oxygen breathing.

In addition to this study of anoxemia alone on Q-$T_c$[38], Yu and his associates[45-47] reported on the effects on the Q-T interval of hypoxic breathing superimposed upon exercise. Although their findings appear at first to be contradictory to the results obtained with anoxemia alone, the exercise factor which may shorten Q-$T_c$[38] impairs the validity of any comparisons of their findings with those here reported.

Since Q-T duration is apparently dependent on cardiac oxygen consumption[37] it is likely that the abnormal prolongation of Q-$T_c$ during a period of anoxia occurs as the result of changed myocardial metabolism incident to relative oxygen deprivation. Thus, the process of repolarization, wherein work is performed, may be delayed.

The term "electrical systole" has been criticized in that systole is a purely mechanical phenomenon.[8] However, the term enjoys widespread usage and indicates the "time required for depolarization and repolarization of the ventricular musculature".[24] Whether electrical and mechanical systole exactly coincide is controversial.[48-53] To investigate this phase of the problem simultaneous phonocardiograms were recorded during most of these anoxemia tests. These observations and the ballistocardiographic findings will be presented in subsequent reports.

The recognized higher values of initial Q-$T_c$ occurring normally in women[36] preclude the use of this method in evaluating female patients until normal values for the Q-T Anoxemia Index have been determined in women.

The prolongation of Q-$T_c$ in the patient exhibiting the hyperventilation syndrome is probably a reflection of reduced ionic calcium, secondary to the increased breathing.[24] Since the test in this patient was positive because of RS-T depression in the limb leads, this cannot be the result of change in heart position in hyperventilation as suggested by Scherf and Schlachman.[54] The positive Levy test in the 24-year-old patient with recent pericarditis is interpreted as "false" in the sense that there is no evidence that the patient had coronary arteriosclerosis. It is quite conceivable, however, that local circulatory embarrassment existing as a sequel to scarring in the myocardium subjacent to the pericardium was brought out and gave rise to the changes noted. This local ischemia did not prolong the Q-T interval, suggesting the heart as a whole did not experience relative oxygen want during the anoxic stress.

In all three groups of patients there are included cases of hypertension and cardiomegaly of various etiologies, although either condition per se tends to prolong Q-T duration. This was done to establish the effects of anoxemia in the presence of these conditions which frequently accompany coronary artery disease. Patients with cardiomegaly and/or hypertension but with no evidence of coronary artery disease may exhibit an initial Q-$T_c$ exceeding 0.480 sec., which would require no increase during anoxia for an abnormal Q-T Anoxemia Index. In this connection, it is noteworthy that great systolic prolongation relative to diastole, by its encroachment upon the diastolic coronary flow period, may be conducive to relative coronary insufficiency.[45]

Digitalis may account for the normal Q-T Anoxemia Index observed in patients with angina pectoris who fell within the normal range, although seven digitalized cases of angina pectoris did have an abnormal Q-T Index. Thus, it appears that some caution must be used in interpreting a negative Q-T response in persons receiving digitalis. Likewise, the presence of a manifest cause of initial Q-T prolongation (electrolyte imbalance, quinidine, myxedema, etc.) would obviously preclude interpretation of initial Q-$T_c$ and its changes in the same manner as when these factors are absent.

The finding of a positive Q-T Anoxemia Index in 89.5 per cent of the patients considered to have angina pectoris, as compared with only 55.2 per cent positive by the Levy criteria, suggests that use of the Q-T Anoxemia Index may increase the sensitivity of the anoxemia test without materially increasing the incidence of false positives. The Levy test is based on a carefully compiled and tested set of empirical criteria which have yielded a minimal incidence of false-positive tests from laboratory to laboratory. Changes in the RS-T segment of the electrocardiogram away from the isoelectric line and changes in the shape, amplitude, and electrical sign of the T wave in various derivations depend upon the spatial orientation of developed areas of injury current or changes in gradients of fundamental ventricular myocardial electrical properties[55] which, short of vector analy-

sis, must be interpreted empirically. The corrected Q-T interval when determined with suitable precautions[41,42] appears to bear a valid relation to the duration of electrical systole and thus directly measures a fundamental myocardial property, that is, the time required for depolarization and repolarization of the heart muscle, and is more nearly independent of spatial considerations. It is, therefore, not surprising that a better separation may be achieved with a criterion based upon corrected Q-T duration than by S-T and T-wave criteria alone.

## SUMMARY

1. The Levy anoxemia test has been studied in forty normal men and ninety-five male patients with reference to alterations in the duration of electrical systole, as measured by the corrected Q-T interval ($Q\text{-}T_c$).

2. Initial $Q\text{-}T_c$ durations were significantly higher in patients with angina pectoris as a group than in controls, confirming previous studies.

The maximal increase in $Q\text{-}T_c$ during the anoxemia test in patients with true angina pectoris was compared with the maximal increase in $Q\text{-}T_c$ in normal subjects and patients with chest pain of noncardiac origin. The prolongation of $Q\text{-}T_c$ was much greater in the patients with angina, the mean values showing highly significant differences. However, the wide range of response among the subjects and the patients precludes the use of this measurement alone to distinguish between normal and abnormal.

4. When the maximal increase in $Q\text{-}T_c$ during the anoxemia test is plotted against the control (initial) $Q\text{-}T_c$ value for all subjects and patients, it is found that an oblique line may be drawn which separates nearly all of the patients with true angina pectoris from nearly all of those without it. The equation representing this line of separation is: 0.480 sec. = (initial $Q\text{-}T_c$) + 2.6 (maximal increase in $Q\text{-}T_c$). For simplicity in clinical application it can be stated that 0.480 is the "upper limit of normal" for men of a value computed by adding 2.6 times the maximal increase of $Q\text{-}T_c$ during anoxia to the initial $Q\text{-}T_c$ duration. The value so determined is termed the "Q-T Anoxemia Index".

5. Of two observed "false-positive" Levy anoxemia tests, one case in which hyperventilation was causative also demonstrated an abnormal $Q\text{-}T_c$ response. The other, in whom the RS-T, T-wave abnormalities are considered a residuum of recent pericarditis, showed a normal "Q-T Anoxemia Index".

6. These observations suggest that the alteration of $Q\text{-}T_c$ duration during the course of the anoxemia test may be an additional aid in distinguishing a normal from an abnormal response since 89.5 per cent of patients considered to have true angina pectoris exhibited positive tests by the Q-T Anoxemia Index criterion, in contrast to only 55.2 per cent positive by the Levy criteria, while the incidence of false positives was not significantly increased.

The authors are indebted to Miss Eva Dorris, R.N., for her invaluable assistance in the calculation and tabulation of the data, as well as her aid in the performance of the anoxemia tests.

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# THE ELECTROCARDIOGRAM IN HEMORRHAGIC FEVER

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## INTRODUCTION

HEMORRHAGIC fever is a disease of probable infectious origin which has been known to western medicine only since it was encountered by the United Nations forces in Korea in 1951. More than 1,500 cases have been reported among United Nations personnel through 1952. The mortality rate in 1951 was approximately 7 per cent, but since then it has been slightly less than 5 per cent. Numerous articles pertaining to various aspects of the disease have appeared in the literature since that time and in some of these electrocardiographic abnormalities have been mentioned.[1-5] However, a comprehensive study of this phase of the disease has not yet been published. During the latter part of 1951, the Osaka Army Hospital served as a center for the treatment of hemorrhagic fever. During that time 300 patients received extensive study at this hospital, the results of which have been reported by one of us.[1] This paper is an extension of that study, for the purpose of presenting a more detailed account of the electrocardiographic findings.

The etiologic agent of the disease is unknown.[6] The course follows a common pattern consisting of three fairly well defined phases[1,2] which have been termed the invasion, toxic, and convalescent stages. The invasion stage usually is of three to five days' duration and is characterized by high fever and mainly symptomatology common to acute febrile illnesses. The toxic stage usually begins just before the fever subsides and continues until the tenth to fourteenth day of illness, although occasionally much longer. Manifestations of this stage may include shock at onset, oliguria, hemorrhagic phenomena, gastrointestinal disturbances, and signs of cerebral toxicity. The convalescent stage usually begins on the tenth to the fourteenth day and lasts from six weeks to four months. It is characterized by easy fatigability, polyuria, and slow return of the ability to concentrate urine and excrete phenolsulfonphthalein satisfactorily.

There are a number of factors in hemorrhagic fever evidenced by pathologic and physiologic findings which might be expected to produce electrocardiographic abnormalities. The pathology of the disease has been reviewed by Hullinghorst and Steer.[7] Cardiac findings include increase in weight, hemorrhage, and focal

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myocarditis. Eleven of 46 hearts examined weighed more than 400 grams. The hemorrhage, which is usually grossly visible, is strikingly localized to the right atrium and is one of the most distinctive pathologic features of the disease. Microscopically, it is observed to be diffusely spread through the subendocardium of this chamber and is associated with engorged and dilated capillaries. There is no reaction to the hemorrhage. The reason for the remarkable localization is not known, but its relative constancy was also noted by Kessler[8] and in the nine fatal cases at this hospital it was grossly visible in seven and microscopically evident in all.[1] Scattered areas of hemorrhage also occur in other parts of the heart, but they are much less marked and are discrete in type. The myocarditis is evidenced by an interstitial infiltration of mononuclear cells which is most prominent in the left atrium and adjacent portions of the ventricles, becoming less so toward the apex.[7] It is much less marked and less frequent than the right auricular hemorrhage, being noted only once in the nine autopsied hearts at this hospital.

Of the disturbed physiologic mechanisms in the disease, two of the most important are vascular instability and renal failure. Vascular instability is manifest by hypotension, most frequent from the fourth to the eighth day of illness. The blood pressure is labile and orthostatic phenomena are observed. The systolic blood pressure falls to shock levels in 10 per cent of the cases[1] and irreversible shock is a common cause of death. Of sixty-one deaths reported by Hullinghorst and Steer,[7] twelve were due to shock. Renal failure is characterized by severe oliguria which usually lasts from three to six days but occasionally longer. The development of uremia depends upon the duration and severity of urine suppression. This is in turn associated with electrolytic disturbances, of which hyperkalemia is the most important from a cardiac standpoint. Hypertension may develop with the uremia and rarely is there evidence of pericarditis. Death was due to uremia in twenty-eight of the sixty-one reported cases.[7]

Probably as a consequence of a combination of the above features as well as a presumed "capillary leakage",[4] pulmonary edema may occur in the final stage. This is aggravated by any tendency to overhydration. Of the sixty-one reported cases, fourteen died wih pulmonary edema, and six of these were associated with uremia.[7]

Because of these various features of the disease affecting the cardiovascular system, a detailed study of the electrocardiographic findings seems appropriate.

## METHOD OF STUDY

For the purpose of this study the electrocardiograms were divided into two major groups. The first group consisted of 147 electrocardiograms recorded on fifty-five patients during the acute phase of the disease (the invasion and toxic stages).[1,2] The second group consisted of 90 electrocardiograms recorded on seventy-eight patients during convalescence. Twelve leads, including the three standard limb leads, unipolar extremity leads, and precordial Leads $V_1$ through $V_6$, were taken in all but a few instances.

Electrocardiograms recorded during the acute phase were taken at the discretion of the ward officers when there was reason to believe an electrocardiogram might prove of clinical value. As a result, they were generally taken on the more severely ill patients, particularly those showing marked oliguria with azotemia, shock states, or clinical findings suggesting a cardiac disturbance such as pulmonary congestion, bradycardia, arrhythmia, or friction rub. One or more electrocardiograms were taken on seven fatal cases, and the autopsy material was available for correlation in each instance.

In an attempt to enumerate the various abnormalities and to correlate them with the day of illness, degree of azotemia, urinary output, cardiovascular manifestations, and pathologic findings, a chart has been prepared describing those cases in which one or more electrocardiograms were considered abnormal (Table I). Serial change, including tracings taken during convalescence when available, was carefully studied. In the table only the abnormal features of the tracings are recorded and the abnormalities in subsequent tracings are not redescribed unless a significant change is noted. Also, the rate and P-R, QRS and Q-T intervals are recorded only when abnormality exists in a given tracing and are not again noted unless a significant change occurs. Ashman and Hull's table is used for the determination of the upper limits of normal of the Q-T interval.[9] The clinical and pathologic data recorded in the "Remarks" column include only positive findings significant from a cardiovascular standpoint. Urinary output records are frequently incomplete but when available are recorded for three days preceding the tracing.

Since severe oliguria and azotemia are common in hemorrhagic fever, the tracings were scrutinized for evidence of hyperkalemia. Particularly important in the diagnosis of this effect, because it is the earliest change, is alteration in the contour of the T waves. In addition to the increased amplitude and pointing of the apices ("peaking"), Levine and associates[10] have stated that the T wave in hyperkalemia may be of normal amplitude but "tent shaped" so that an imaginary plumb line dropped from the apex forms approximately equal angles. This is in contrast to the normal T wave which is "asymmetrical with a gradual ascending slope, a rounded summit, and an abrupt descent".[10] Also, the T wave in hyperkalemia presents an unusually narrow base which is a result of increased amplitude and the acute angle at the apex.

In this study, for the purpose of presentation, the T waves have been graded according to the degree with which they suggest hyperkalemic effect. This effect is most readily noted in the precordial leads.[11] Kossman and Johnston have recorded the limits of normal amplitude of the precordial T waves,[12] but because of the importance of contour simple measurement does not sufficiently describe the hyperkalemic effect. To circumvent the lack of absolute criteria for the electrocardiographic diagnosis of hyperkalemia, reproduced examples are shown (Fig. 1) of four types of T waves which vary progressively in the degree with which they suggest hyperkalemic effect. The T waves suggestive of hyperkalemic effect in the tracings studied are accordingly classified as K-1, K-2, K-3 or K-4, depending

upon which example they most closely resemble. T waves in K classes 3 and 4 are sufficiently characteristic that their presence is indicative of hyperkalemic effect. K classes 1 and 2 include the "tent shaped" T waves of Levine and associates.[10] The K class 2 type of T wave in a single tracing is suggestive but not diagnostic. The T wave of K class 1 type was recorded in the table only when a series was available for comparison, and it appeared with azotemia and oliguria or became normal with a falling blood nonprotein nitrogen and diuresis. Under such circumstances, both the K class 1 and 2 types were considered as probably indicative of hyperkalemia. Since serial electrocardiograms were not recorded in many cases, the incidence of hyperkalemic effect reported in this study is probably less than could be diagnosed if serial tracings had been taken in all cases.

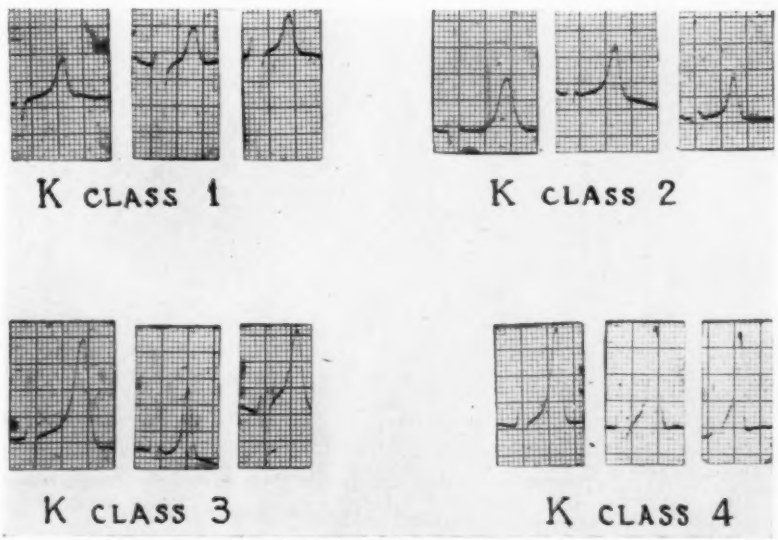


Fig. 1.—Examples of tracings with T waves varying in the degree with which they suggest hyperkalemic effect. Criteria for classification are described in "Method of Study."

Facilities were not available for performing serum potasium determinations to compare with the electrocardiograms. Although this is unfortunate, it does not seriously mitigate the value of the study, since it has been pointed out that the clinical syndrome of potassium intoxication is more closely related to the electrocardiogram than to the level of serum potassium.[13] The concentration of other ions, particularly sodium and calcium, modifies or aggravates the effect of potassium upon the electrocardiogram, while "the electrocardiogram records the totality of the effects of the ionic environment acting at the surface of the heart muscle cell and reflects faithfully the reaction of the cardiac muscle".[13] Therefore, in our discussion of the electrocardiograms reference has been made to this abnormality as "hyperkalemic effect" rather than hyperkalemia per se.

TABLE I. DESCRIPTION OF 27 CASES WITH ELECTROCARDIOGRAPHIC ABNORMALITIES DURING THE ACUTE PHASE OF HEMORRHAGIC FEVER

| CASE NO. | DAYS OF ILLNESS | BLOOD NPN | ECG ABNORMALITIES | REMARKS |
|---|---|---|---|---|
| 2. | 7 | 92 | Rate 40. | Sinus bradycardia. Urine volume not recorded. |
| 3. | 9 | | Rate 35; T's, K-2. | Sinus bradycardia; hyperkalemic effect suggested by T waves. Urine vol. 400 and 1,900 c.c. on 7th and 8th days. |
| | 12 | 60 | | |
| 4. | 8 | | T's, K-3. | Hyperkalemic effect indicated by T waves. Urine vol. 50 c.c. or less from 8th to 10th day. Death on 9th day with toxic delirium. Necropsy revealed scattered areas of hemorrhage in wall of right auricle but no significant evidence of myocarditis. Heart weight = 320 grams. |
| | 9 | 91 | | |
| 5. | 5 | 130 | Rate 50; QRS, 0.12; Q-T, 0.56 (ULN 0.45); T's K-3. | Sinus bradycardia; hyperkalemic effect indicated by T waves, QRS and Q-T prolonged. Urine vol. 140, 675, 1,250 and 900 c.c. from 4th to 7th days. |
| | 6 | 118 | No significant change. | |
| | 7 | 62 | Rate 42. No significant change. | |
| 7. | 10 | 100 | T in 1 diphasic, T in 2,3, $aV_F$, $V_5$, $V_6$ slightly inverted. | (Fig. 2) Nonspecific negative T-wave changes on 10th day which accompanied clinical shock. Subsequent tracings showed increasing hyperkalemic effect. Urine vol. 2,300; 2,100; 1,825; 2,300; 2,950; 1,800; and 1,900 c.c. from 7th through 13th day. |
| | 11 | 180 | T's now upright except diphasic T in 1 and $V_6$. T's $V_{2,3}$ K-1. | |
| | 13 | | T's K-4. | |
| | 16 | 206 | | |
| 9. | 15 | 202 | Auricular bigeminy. T's, K-3. | (Fig. 5) Auricular premature contractions with intermittent auricular tachycardia and hyperkalemic effect indicated by T waves. Urine vol. 75; 550; 1,440; 1,000; 1,080 c.c. from 12th through 16th day. Chest roentgenogram on the 15th day revealed generalized cardiac enlargement. Death on 17th day in uremia with associated pulmonary congestion. Necropsy revealed diffuse hyperemia and hemorrhage in wall of right auricle, no significant evidence of myocarditis. Heart weight = 350 grams. |
| | 16 | 285 | Auricular bigeminy with runs of auricular tachycardia, T's K-1. | |
| 12. | 8 | 214 | Q-T, 0.41 (ULN, 0.40); T's, K-2. | Hyperkalemic effect probably indicated by T waves which return to normal with subsidence of oliguria. Urine vol. 400; 300; 500; 1,000; 1,200; 1,700 from 7th through 12th day. Renal function was normal on 40th day. |
| | 10 | 170 | Q-T, 0.40 (ULN, 0.40); T's K-2 or 3. | |

| | | | | |
|---|---|---|---|---|
| | 11 | | None. | |
| | 12 | | Q-T, 0.42 (ULN, 0.39) | |
| | 40 | | None. | |
| 13. | 7 | 146 | | Hyperkalemic effect indicated by markedly abnormal T waves on 10th and 11th days, which disappear with convalescence. Urine vol. 400, 0, 0, 0, 1,750 from 7th through 10th day. Renal function was normal on 77th day. |
| | 10 | | T's K-4. | |
| | 11 | | Q-T, 0.40 (ULN, 0.38). T's K-4. | |
| | 13 | 266 | | |
| | 77 | | None. | |
| 17. | 7 | 79 | None. | Hypokalemic effect is suggested in this tracing by rounding and decrease in amplitude of T waves with prolongation of Q-T interval during diuresis. Urine vol. 350 and 650 c.c. on 7th and 8th days, and 3,100; 3,000; and 2,900 c.c. from 12th through 15th days. |
| | 8 | 94 | None. | |
| | 15 | 42 | Q-T, 0.44 (ULN, 0.41). T waves are rounded and decreased in amplitude. | |
| 18. | 8 | 171 | T's K-2. | Hyperkalemic effect probably indicated by T waves which return to normal with convalescence. Urine vol. 600; 2,400; and 2,600 c.c. from 8th through 10th day. Renal function normal on 38th day. |
| | 9 | 190 | T's K-2. | |
| | 10 | 141 | T's K-2. | |
| | 38 | | T's normal. | |
| 19. | 8 | 120 | Q-T, 0.39 (ULN, 0.37). T's, K-3. | Hyperkalemic effect indicated by T waves which return to normal with convalescence. Urine vol. 500 and 1,800 c.c. on 7th and 8th days. Renal function normal on 39th day. |
| | 39 | | None. | |
| 21. | 5 | | P-R, 0.22, Q-T, 0.44 (ULN, 0.40). T's, K-2. | Hyperkalemic effect suggested by T waves. Urine vol. 200; 1,030; 1,530; and 2,700 c.c from 5th through 8th day. |
| | 8 | 147 | | |
| 22. | 7 | 153 | | (Fig. 3) Advanced hyperkalemic effect on 8th and 9th days with complete disappearance on 10th, concomitant with diuresis. Nonspecifically depressed T waves on 10th day. Urine vol. 300; 1,100; and 2,300 c.c. from 7th through 9th day. Death on 10th day with terminal fever, convulsions and pulmonary edema. Necropsy revealed severe pulmonary edema, diffuse hyperemia and hemorrhage in wall of right auricle; no significant evidence of myocarditis. Heart weight = 450 grams. |
| | 8 | | Rate 133, Q-T, 0.30 (ULN, 0.29). Questionable notching P in 1 and $aV_F$; prominent S in 2,3, $V_1$ to $V_6$. T's, K-3. Clockwise rotation in vertical heart. | |
| | 9 | 220 | Rate 133. P's flattened and absent in $V_{2,3,4,5,6}$. QRS, 0.10, T's, K-3 or 4. Clockwise rotation increased. | |

TABLE I. DESCRIPTION OF 27 CASES WITH ELECTROCARDIOGRAPHIC ABNORMALITIES DURING THE ACUTE PHASE OF HEMORRHAGIC FEVER (CONT'D)

| CASE NO. | DAYS OF ILLNESS | BLOOD NPN | ECG ABNORMALITIES | REMARKS |
|---|---|---|---|---|
| | 10 | | Rate 125. Q-T, 0.28 (ULN, 0.30). P's normal, T's show loss of hyperkalemic effect and are abnormally flat in $V_{4,5,6}$. | |
| 27. | 7 | 91 | None. | Hyperkalemic effect is suggested by peaked T waves during oliguria which become abnormally rounded during diuresis (hypokalemia?). Against hypokalemia is the absence of Q-T prolongation. Urine vol. 1,400; 500; 400; 400; 800; 1,900; 4,100; 2,650; 3,600; 3,800 from 6th through 15th day. |
| | 8 | 125 | QRS, 0.12, T's, K-1. | |
| | 15 | 54 | QRS, 0.10, change in contour of T waves with abnormally rounded summits. T in $V_6$ flat. | |
| 28. | 8 | 168 | | Hyperkalemic effect probably indicated by T waves which revert to normal with convalescence. P-R and Q-T intervals shorten during convalescence. Urine vol. 100 and 150 c.c. on 8th and 9th days. |
| | 9 | | P-R, 0.20, Q-T, 0.40 (ULN, 0.40). T's, K-2. | |
| | 12 | 164 | | |
| | 40 | | P-R, 0.16, Q-T, 0.30 (ULN, 0.34). T's normal. | |
| 30. | 3 | 42 | T-2 diphasic; T in 3, $aV_F$ inverted, R-T in $V_{5,6}$ slightly depressed. Vertical heart. | (Fig. 4) Nonspecific negatively directed T-wave changes on 3d, 4th and 5th days. Patient febrile at that time. BP 88/74 mm. Hg on 5th day. Hyperkalemic effect indicated by progressive changes in T waves from 7th to 11th day with T waves becoming abnormally rounded on 17th day. Prolonged Q-T on latter date coincided with diuresis and may have been a hypokalemic effect since convalescence. Urine vol. 960; 500; 60; 800; 500; 1,910; 1,335; and 2,200 c.c. from 4th through 11th day and 2,380; 2,100; 2,475; and 3,700 from 14th through 17th day. Renal function normal by 50th day. |
| | 4 | | No change. | |
| | 5 | | Q-T, 0.36 (ULN, 0.34). T's in 2,3, and $aV_F$ less less negative. | |
| | 6 | 102 | Q-T, 0.40 (ULN, 0.38). T's normal. | |
| | 7 | | Q-T, 0.43 (ULN, 0.40). T's, K-1. | |
| | 8 | 150 | No change. | |
| | 9 | | No change. | |
| | 10 | 186 | | |
| | 11 | 129 | Q-T, 0.40 (ULN, 0.37). T's, K-3. | |

| | | | | |
|---|---|---|---|---|
| | 17 | 129 | Q-T, 0.40 (ULN, 0.39). T's abnormally rounded | |
| | 50 | | None. | |
| 31. | 6 | | T's, K-2. | Hyperkalemic effect suggested by T waves, but contour of T waves shows no significant variation in this series. Urine vol. 1,820 and 2,200 c.c. on 10th and 11th days. Creatinine 8.7 mg. per cent on 7th day. |
| | 7 | 87 | T's, K-2. | |
| | 10 | 110 | | |
| | 12 | | T's, K-1 or 2. | |
| | 14 | 50 | | |
| 34. | 9 | 160 | | (Fig. 3) Advanced hyperkalemic effect with typical T waves, LBBB pattern, and absent P waves. Patient died at 7:30 A.M. on 11th day with pulmonary congestion and cardiac arrest indicated by terminal respiration without an audible heart beat. Necropsy revealed diffuse hemorrhage in right auricle, no evidence of myocarditis. Urine vol. 200; 400; 0; 0; 1,400 and 3,600 c.c. from 5th through 10th day. Heart weight = 325 grams. |
| | 10 (9 AM) | | P's absent, LBBB pattern, QRS, 0.14, T-1 diphasic, other T's, K-3. Q-T, 0.45 (ULN, 0.41). | |
| | 10 (5 PM) | | No change, except T's have changed to K-1 type. | |
| 35. | 7 | 128 | QRS, 0.14. RBBB pattern. T's normal. | (Fig. 5) Advanced hyperkalemic effect with typical T waves and increased QRS and Q-T durations which increase with oliguria and azotemia and shorten in convalescence. Right bundle branch block present in all tracings. Urine vol. 99; 210; 75; 425; 220; 1,350; 1,500; 3,900; 5,055; 4,090 c.c. from 7th through 16th day. Renal function normal on 65th day. |
| | 8 | | QRS, 0.14. RBBB, T's, K-1. | |
| | 9 | | QRS, 0.16. RBBB, T's K-2. | |
| | 10 | 175 | QRS, 0.17. RBBB, Q-T, 0.44 (ULN, 0.39). T's K-3. | |
| | 11 | | No change. | |
| | 12 | | QRS, 0.17. RBBB, Q-T, 0.41 (ULN, 0.38). T's K-1. | |
| | 13 | | QRS, 0.15. RBBB, Q-T 0.42 (ULN, 0.36). T's, normal. | |
| | 14 | | QRS, 0.14. RBBB, Q-T, 0.38 (ULN, 0.36). T's, normal. | |
| | 16 | 89 | QRS, 0.12. RBBB, Q-T, 0.40 (ULN, 0.36). T's, normal. | |
| | 65 | | QRS, 0.12. RBBB, Q-T, and T's normal. | |

TABLE I. DESCRIPTION OF 27 CASES WITH ELECTROCARDIOGRAPHIC ABNORMALITIES DURING THE ACUTE PHASE OF HEMORRHAGIC FEVER (CONT'D)

| CASE NO. | DAYS OF ILLNESS | BLOOD NPN | ECG ABNORMALITIES | REMARKS |
|---|---|---|---|---|
| 37. | 13 | 225 | | Hyperkalemic effect probably indicated by T waves during azotemia which become normal with convalescence. Q-T interval also prolonged during azotemia. Urine vol. 500; 300; 0; and 1,450 c.c. from 11th through 14th day. Renal function normal on 82nd day. |
| | 14 | | Q-T, 0.45 (ULN, 0.40). T's, K-2. | |
| | 82 | | None. | |
| 38. | 12 | 79 | T's, K-2. | Hyperkalemic effect probably indicated by T waves during azotemia which become normal with convalescence. Urine vol. not recorded. Renal function normal on 68th day. |
| | 68 | | T's, normal. | |
| 43. | 11 | 145 | Rate 78, Q-T, 0.40 (ULN, 0.38). T in 1, $V_{2,3,4,5,6}$ inverted. | (Fig. 2) Nonspecific negative T waves on 11th and 12th days. Q-T prolonged on 11th but normal on 12th and 13th. |
| | 12 | 124 | Rate 140, Q-T, 0.26 (ULN, 0.28). T in 1, less inverted. V leads not taken. | Patient developed pulmonary edema on 11th day following 1,000 c.c. I.V. infusion and failed to respond to digitalis. Urine vol. of 850; 2,200; and 2,115 c.c. on 11th, 12th, and 13th days, respectively. No hypotension present during 5½ days of hospitalization. Death occurred on 14th day. Necropsy revealed severe scattered hemorrhages in right auricle and mild myocarditis evidenced by foci of mononuclear cell infiltration throughout myocardium. Heart weight = 375 grams. |
| | 13 | 118 | Rate 166, Q-T, 0.22 (ULN, 0.28). T in 1,2,3 upright but summits abnormally round. V leads not taken. | |
| 44. | 5 | | Rate 100, otherwise normal. | Hyperkalemic effect suggested by change in contour of T waves in the precordial leads on the 6th day but associated with nonspecific negative T waves in the extremity leads on the same day. Urine vol. 400; 100; 360; and 500 c.c. from 5th through 8th day. Patient developed 3 severe episodes of shock from 4th to 9th day. Death occurred in shock on 9th day. Necropsy showed marked pulmonary edema and hemorrhage into wall of right auricle of heart, and interstitial edema and foci of degeneration throughout the myocardium but absence of mononuclear cell infiltration. Heart weight = 320 grams. |
| | 6 | | Rate 120, T in 2,3,$aV_F$ inverted. Precordial T's, K-1. | |
| | 7 | 144 | Rate 110, T in 2 upright, in 3 inverted in $aV_F$ flat. Precordial T's, K-1. | |
| 47. | 6 | 114 | Q-T, 0.33 (ULN, 0.36). R-T in $V_2$ elevated 3 mm. T's, K-2. | (Fig. 5) Hyperkalemic effect indicated by marked alteration of T-wave contour during azotemia, with subsidence during an initial fall coincident with onset of diuresis beginning on the 10th day and a reappearance with later increase of azotemia. The Q-T interval was also prolonged during the azotemia. Urinary vol. 60; 0; 0; 0; 460; 600 and 525 c.c. from the 3rd to the 9th day, and above 1,600 c.c. with a daily average of 2,670 c.c., from the 10th through the 24th day. In spite of this the period of azotemia was unusually prolonged in this case. A moderate hypotension was noted from the 3rd to 5th day. |
| | 7 | 132 | Q-T, 0.40 (ULN, 0.37). T's, K-4. | |
| | 8 | 121 | Q-T, 0.28 (ULN, 0.31). R-T in $V_2$ now isoelectric. T's, K-4. | |

| | | | | |
|---|---|---|---|---|
| | 9 | 158 | Q-T, 0.38 (ULN, 0.35). T's unchanged. | |
| | 10 | 158 | Q-T, 0.30 (ULN, 0.31). T's, K-3. | |
| | 11 | | Q-T, 0.38 (ULN, 0.36). T's unchanged. | |
| | 15 | 190 | Q-T, 0.28 (ULN, 0.31). T's unchanged. | Uremic pericarditis also diagnosed in this case on the basis of a friction rub on the 9th day. Confirmatory RS-T segment elevation also present, but subsequent to the time that the friction rub was heard. |
| | 17 | 185 | Q-T, 0.30 (ULN, 0.35). T's normal. | |
| | 18 | 91 | T's further decreased in height and summits rounded. | |
| | 22 | 125 | RS-T segment elevated 7 mm. in $V_2$ and 2 mm. in $V_1$. T's, K-2. | |
| | 24 | 130 | RS-T segment elevated 3 mm. in $V_2$. T's, K-3. | |
| | 39 | 50 | RS-T segment elevated 3 mm. in all precordial leads. T's normal. | |
| 50. | 7 | | Rate 43. T's, K-1 to K-2. | Sinus bradycardia; hyperkalemic effect probably indicated by T waves which become normal during convalescence. Urine vol. 1,400; 2,320; 4,800; 3,750 from 7th through 10th day. Renal function normal on 26th day. |
| | 10 | 64 | | |
| | 26 | | Rate 75. Definite loss of T-wave K effect. | |
| 51. | 14 | 37 | T in 2,3, $aV_F$ flat. U waves abnormally prominent. Vertical heart. | Nonspecific T-wave changes with prominent U waves on 14th day. May possibly be hypokalemic effect, but Q-T interval within normal limits. Urine vol. ranged from 1,200 to 2,950 c.c. from 8th through 21st day. |
| | 17 | | T's normal. U waves absent. | |
| | 21 | | Normal. | |
| 55. | 5 | 58 | Q-T, 0.42 (ULN, 0.40). Horizontal heart with large $S_3$. T in 3, $V_{1,2,3,4}$ inverted. T in 2, $aV_F$, $V_{5,6}$ flattened. | (Fig. 6) Marked nonspecific T-wave abnormalities during acute phase with an extremely slow return to normal in convalescence. Q-T interval greatly prolonged at time T waves most abnormal. Q waves and RS-T segments remained within normal limits. Clinical evidence of heart involvement was absent. Patient was afebrile after 7th day. Moderate shock with BP of 90/60 mm. Hg on 7th, 3 convulsions with BP of 200/120 mm. Hg on 9th, severe hemorrhagic diathesis present from 5th to 12th day. Exact urine volumes are not available but there was moderate oliguria from th to 10th day. |
| | 6 | 94 | | |

TABLE I. DESCRIPTION OF 27 CASES WITH ELECTROCARDIOGRAPHIC ABNORMALITIES DURING THE ACUTE PHASE OF HEMORRHAGIC FEVER (CONT'D)

| CASE NO. | DAYS OF ILLNESS | BLOOD NPN | ECG ABNORMALITIES | REMARKS |
|---|---|---|---|---|
| | 12 | 131 | T in 2,3,aV$_F$, V$_{1,2,5}$ deeply inverted with symmetrical limbs. | As late as 117th day patient's urine concentration by Fishberg method reached a specific gravity of only 1.017. ECG changes may have been due to hemorrhage into the myocardium. |
| | 16 | 103 | Q-T, 0.44 (ULN, 0.37). T in 1, 2, 3, aV$_F$, V$_{4,5,6}$ all slightly inverted. R in V$_5$ unusually low amplitude. | |
| | 20 | 38 | T in 2,3,aV$_F$ more deeply inverted. | |
| | 27 | | T in 2,3,aV$_F$ and V$_5$ unchanged. T in V$_4$ now upright. T in V$_6$ flat. | |
| | 30 | | T in V$_5$ less deeply inverted. R in V$_5$ taller. | |
| | 39 | 17 | T's less inverted. | |
| | 44 | | T's less inverted. T in V$_6$ now upright. | |
| | 51 | | Q-T, 0.40 (ULN, 0.37). T in 2 less inverted. Precordial T's now normal. R/S ratio progresses normally across precordium. | |
| | 59 | | Q-T, 0.38 (ULN, 0.39). T in 3 and aV$_F$ remain inverted. | |
| | 63 | | T in 2 slightly diphasic. Prominent S$_2$ and horizontal position of heart remain. | |

NPN—Nonprotein nitrogen, ULN—Upper limit of normal. K-1, 2, 2, 4-degree of hyperkalemic effect. (Fig. 1.).

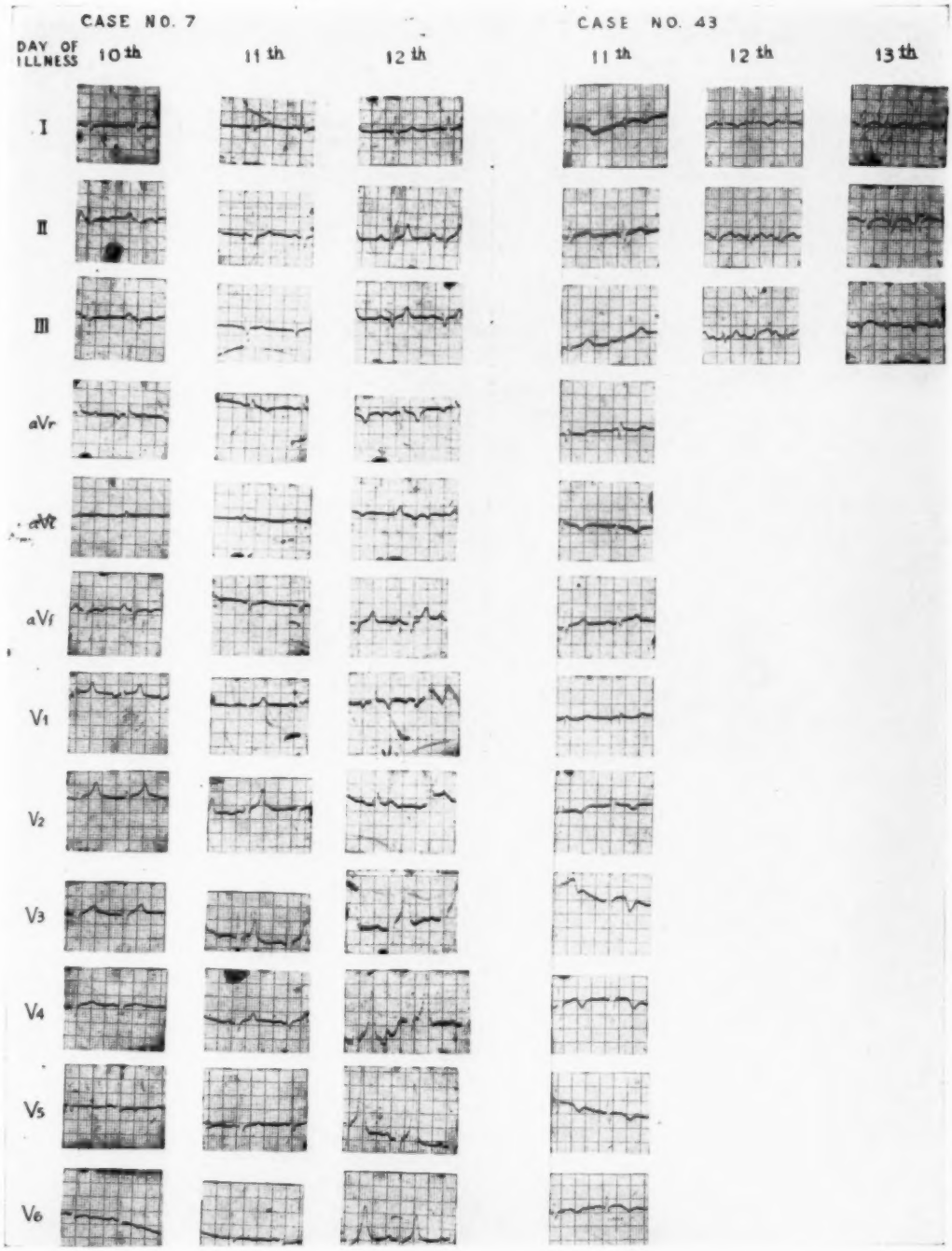


**Fig. 2. (Case 7).—Nonspecific negative T-wave changes on the tenth day accompanying clinical shock. Subsequent tracings demonstrate increasing hyperkalemic effect in the absence of oliguria (average daily urine output of 2,170 c.c. for the preceding 7 days).**

**(Case 43).—Fatal case demonstrating nonspecific negative T-wave changes on the eleventh and twelfth days which subside on the thirteenth day, one day before the patient died. This was the only case in the series in which myocarditis was demonstrated at autopsy.**

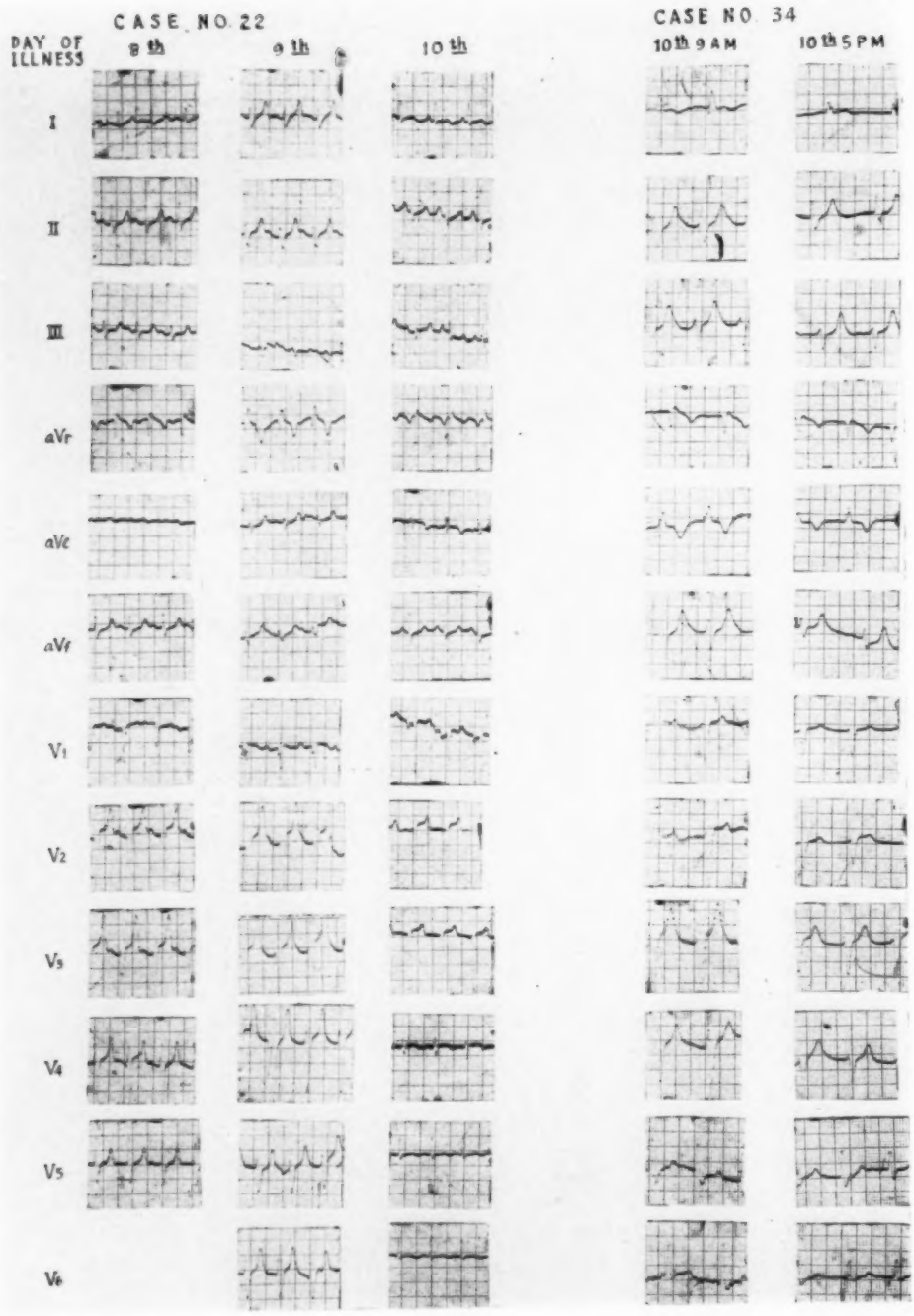


Fig. 3. (Case 22).—Fatal case demonstrating increasing advanced hyperkalemic effect on the eighth and ninth days, manifest by flattening of the P waves, abnormal T-wave contour, prolongation of the QRS complex, and clockwise rotation of the heart. On the tenth day, shortly before death, there was subsidence of the hyperkalemic effect and the appearance of nonspecific negative T-wave changes.

(Case 34).—Fatal case demonstrating advanced hyperkalemic effect in two tracings recorded the day before death, manifest by abnormal T-wave contour, absent P waves, and a left bundle branch block pattern. The hyperkalemic effect of the T waves is less in the second of these tracings.

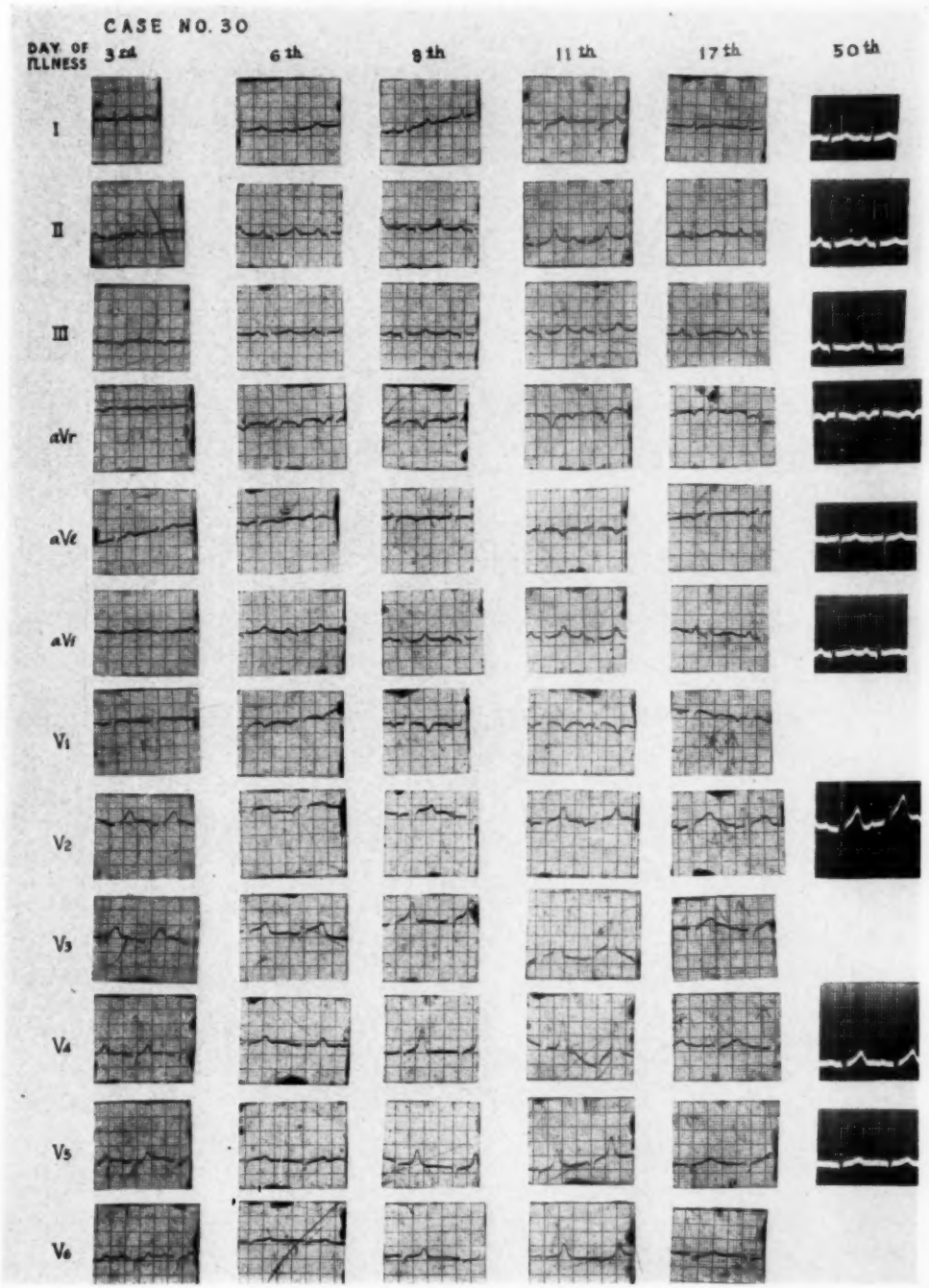


Fig. 4. (Case 30). —Nonspecific negative T-wave changes during the febrile stage on the third day. The tracing on the sixth day is normal with increasing hyperkalemic effect of the T waves becoming apparent following oliguria on the eighth and eleventh days. By the seventeenth day the abnormal T-wave contour has subsided, but there is still Q-T prolongation (hypokalemia ?). The tracing on the fiftieth day is normal.

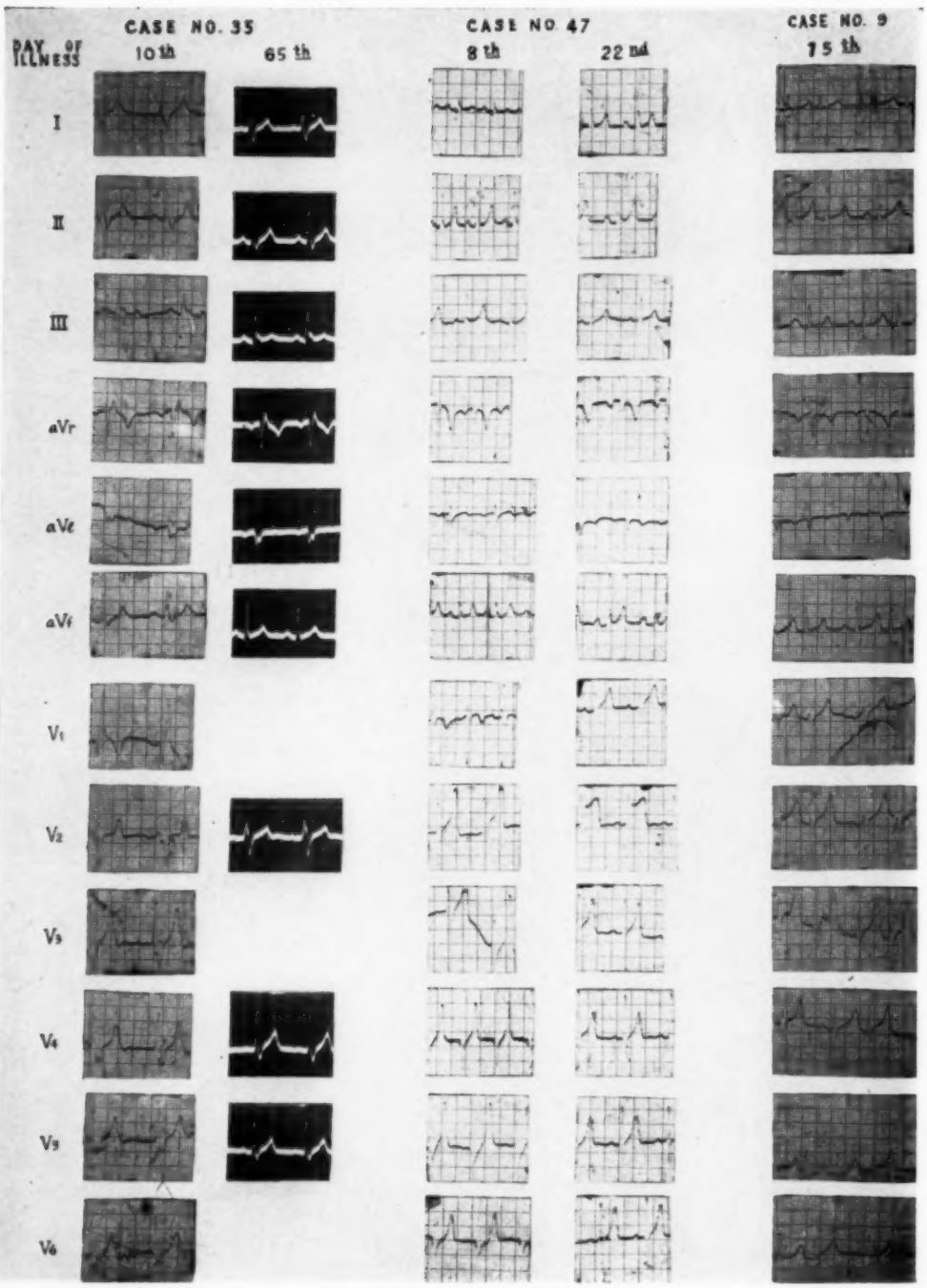


Fig. 5. (Case 35).—Right bundle branch block pattern associated with hyperkalemic effect of the T waves on the tenth day, but persisting late into convalescence after the hyperkalemic effect had disappeared.

(Case 47).—Hyperkalemic effect of the T waves on the eighth day. The duration of azotemia was unusually prolonged in this case and uremic pericarditis was diagnosed on the basis of a friction rub on the ninth day and RS-T segment elevation in Lead $V_2$ on the twenty-second day.

(Case 9).—Fatal case demonstrating multiple auricular premature beats and hyperkalemic effect of the T waves.

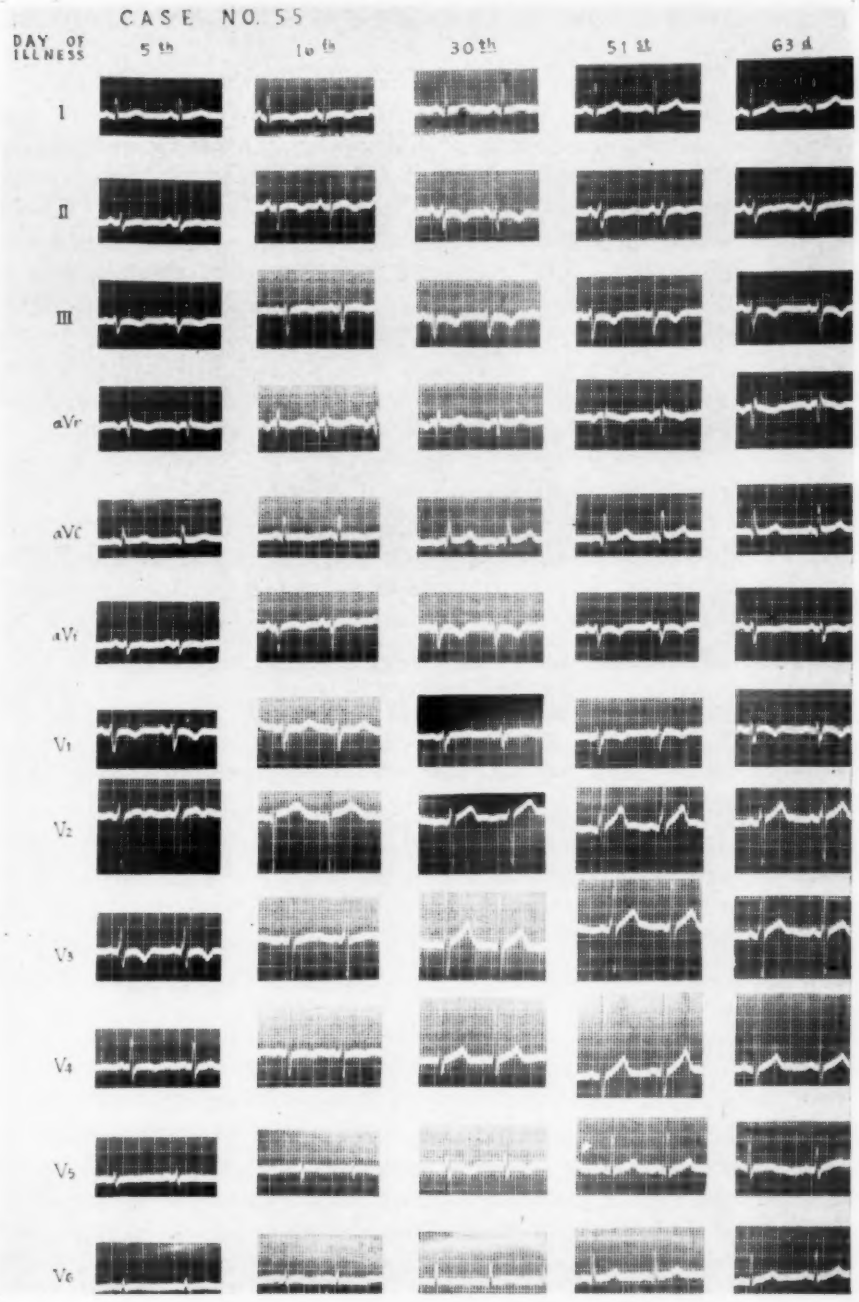


**Fig. 6. (Case 55).—Nonspecific but marked negative T-wave changes during the acute phase of illness and persisting late into convalescence. The tracing on the sixty-third day of illness is still slightly abnormal, although the series shows a definite progression towards normal. Extensive hemorrhage into the posterolateral wall of the left ventricle is offered as a likely explanation for the abnormalities.**

Electrocardiograms were taken on seventy-eight cases during the convalescent stage of hemorrhagic fever, from the twenty-first to the one hundred and twentieth day after onset of illness. In eighteen of these cases, tracings were also recorded during the acute phase of the illness and are, therefore, also considered in that portion of the study. In one other case electrocardiograms were taken during the acute phase of the disease at another medical installation, but since the early tracings were not available to us the case is not included in the acute series. With the exception of this last patient who had auricular fibrillation, the patients had neither signs nor symptoms of cardiac disturbance, nor was there residual evidence of the disease except for unsatisfactory urine concentration ability, reduced phenolsulfonphthalein excretion, weakness, weight loss, and other minor complaints. Most cases were selected at random to determine whether or not electrocardiographic findings were present during this stage of the disease.

## RESULTS AND DISCUSSION

*Electrocardiograms Recorded During The Acute Phase.*—The electrocardiograms taken during the acute phase of hemorrhagic fever were abnormal or suggestively abnormal in one or more tracings in twenty-seven of the fifty-five cases studied. These abnormalities are summarized as follows:

1. Hyperkalemic effect indicated by K class 3 or 4 type T waves with or without other characteristic findings— 11
2. Hyperkalemic effect probably indicated by K class 1 or 2 type T waves which were present during and which disappeared after the period of azotemia— 8
3. Hyperkalemic effect suggested by K class 2 type T waves without other characteristic findings or serial change in T waves— 3
4. Prolongation of the Q-T interval during oliguria— 11
5. Prolongation of the Q-T interval during diuresis— 4
6. Sinus bradycardia— 4
7. Auricular premature beats— 1
8. Nonspecific negative T-wave abnormalities— 9
9. Right bundle branch block— 1
10. Left bundle branch block— 1
11. Abnormal RS-T segment elevation— 1

Electrocardiographic changes consistent with hyperkalemia were the most common abnormalities observed. The electrocardiograms in four (Cases 5, 22, 34, and 35) of the eleven cases which revealed K class 3 or 4 T waves also included changes characteristic of advanced hyperkalemia such as P-wave flattening and and disappearance, P-R and QRS interval prolongation and clockwise rotation. U waves and disintegration of the ventricular complexes in hyperkalemia, as reported by Levine and associates,[15] were not noted; the systemic syndrome of potassium intoxication[11,13] was observed in only one patient (Case 34).

Electrocardiographic evidence of hyperkalemia was quite definite in four (Cases 4, 9, 22, and 34) and was suggested in one (Case 44) of the seven fatal cases studied. Advanced changes were present in two of these (Cases 22 and 34), but in each the changes became less marked in subsequent tracings taken prior to death. It is difficult to decide to what extent hyperkalemia contributed to the

death of these patients. In this regard it is interesting that Hoff and associates[14] were able to produce temporary cardiac arrest in dogs by stimulating the vagus nerve even when the serum potassium was but slightly elevated.

The timing and frequency of the hyperkalemic pattern was generally related to the duration and degree of oliguria and the resultant azotemia (Table I). This is in accordance with the usual findings in renal insufficiency.[13] However, certain exceptions were noted. In Case 31 the T waves suggested hyperkalemic effect and in Case 38 they probably indicated this effect on days when the blood nonprotein nitrogen levels were but 89 and 79 mg. per 100 c.c., respectively. Also, six of the fifty-five patients studied failed to demonstrate electrocardiographic evidence of hyperkalemia in any tracing, even though the concomitant blood nonprotein nitrogen levels were above 150 mg. per 100 c.c. As might be expected, there was frequently a time lag of one or two days between the onset of diuresis and the disappearance of hyperkalemic effect on the electrocardiogram, as well as the subsidence of azotemia (Cases 5, 18, 30, and 47). However, Case seven provides a striking exception to oliguria as a necessary prerequisite for the development of hyperkalemic effect. In this case the characteristic change appeared even though the daily urine output had averaged 2,170 c.c. for the preceding seven days. The blood nonprotein nitrogen also continued to rise during this period.

Recently explanations for the variable effects of serum potassium concentrations on the electrocardiogram have been presented in the literature.[12,13] The effect of other electrolytes is most important. A low serum sodium and, to a lesser extent, hypocalcemia and acidosis enhance the hyperkalemic effect, while normal values of each antagonize it. Both hypocalcemia and hyponatremia have been reported in hemorrhagic fever.[3,4] Another factor to be considered is the amplitude of the T waves when the serum potassium is normal. If the T wave is abnormally low as with left ventricular hypertrophy or if there is diminutive projection of the T-wave vector upon the precordial leads (where the T-wave changes are most prominent in hyperkalemia[11]), the effect of elevated serum potassium may be lessened.[10]

Two other factors are particularly important in hemorrhagic fever and probably increase the degree of hyperkalemia during the oliguric phase and thereby affect the electrocardiogram. These are (1) increased catabolism produced by the disease which results in release of potassium into the serum, and (2) profound dehydration which increases the potassium concentration in the reduced extracellular compartment.

Prolongation of the Q-T interval was observed in thirteen cases during oliguria and in four cases during diuresis. Only two (Cases 43 and 55) of the thirteen cases showing a prolonged Q-T interval during the oliguric phase failed to reveal electrocardiographic changes of hyperkalemia; but in two others (Cases 30 and 35) hyperkalemic changes were absent in certain tracings in which the Q-T interval remained prolonged. According to Merrill and associates[13] prolongation of the Q-T interval can occur from advanced hyperkalemia alone, but that explanation does not appear statisfactory in these cases since most of them did not exhibit other electrocardiographic evidence of advanced hyperkalemia.

Hypocalcemia, which has been reported during azotemia in hemorrhagic fever,[3] or possibly myocarditis, may better explain this abnormality in the majority of the cases.

Hypokalemia may occur during severe diuresis in hemorrhagic fever[3,4] and should, therefore, be considered as a possible cause of the Q-T prolongation in the four cases in which it was noted during diuresis. In Cases 17 and 30 there was associated abnormal rounding of the T waves but in neither of these, nor in the other two cases, was the urinary output unduly high, nor was RS-T segment depression demonstrated.

Only five cases in this series demonstrated disturbed impulse formation electrocardiographically. Multiple auricular premature beats were observed in one case (Case 9). Four cases (Cases 2, 3, 5, and 50) revealed sinus bradycardia. It should be mentioned, however, that clinically the radial pulse rate fell to less than sixty beats per minute in 28 per cent of 300 cases studied at this hospital.[1] This was most frequently noted during the second and third week of illness. Sinus bradycardia occurs with advanced hyperkalemia,[13] and there was some evidence of hyperkalemic effect in three of the four cases studied, but in none was it advanced. Since hyperemia and hemorrhage in the wall of the right auricle constitute an almost constant pathologic feature of the disease,[1,7] the rare presence of auricular arrhythmia is quite surprising. Also, evidence of P-wave abnormality was absent, except that two cases (Cases 22 and 34) with advanced hyperkalemia revealed a disappearance of the P waves and a previous tracing in one of these (Case 22) showed questionable notching of the P waves. Perhaps, as might be suggested by the lack of evidence of reaction to hemorrhage, the pathologic changes in the right auricle may be only a terminal premortem event and may not occur in the usual patient who recovers.

Nonspecific negative T-wave changes were observed in only nine cases in this series and usually they were mild and transitory. These changes occurred in three (Cases 22, 43, and 44) of the seven fatal cases studied electrocardiographically. The relative infrequency of nonspecific negative T-wave abnormalities is interesting in view of the number of mechanisms in hemorrhagic fever which would be expected to produce this change. These include vascular instability, pulmonary congestion, hypertension, myocarditis, and occasionally hypokalemia during diuresis. Since the final representation of the T wave in the electrocardiogram is the composite result of various factors, perhaps the frequent hyperkalemic effect neutralizes the tendencies to T-wave negativity which has been proposed as occurring in uremia by Langendorf and Pironi, according to Levine and associates.[10] The electrocardiograms in three of the nine cases (Cases 7, 30, and 44) which revealed nonspecific negative T waves were recorded during clinical shock. In one (Case 34) the T-wave change was present as a part of the pattern of bundle branch block. In one (Case 43) pathologic study revealed a mild myocarditis. The T-wave changes in the remaining four cases cannot be fully explained. Since the change occurred during diuresis in two of these cases (Cases 27 and 51), the possibility of hypokalemia is suggested, but the Q-T interval in both was within normal limits. Pathologic examination in another of these (Case 22) failed to

reveal any evidence of myocarditis. The fourth case (Case 55), in which the most markedly inverted T waves of the study were observed, had an extremely protracted and stormy course with severe shock and prominent hemorrhagic manifestations. In this case the T waves were still slightly depressed 63 days after onset of the illness. Extensive hemorrhage into the posterolateral portion of the ventricular myocardium is a likely possibility in this case.

Bundle branch block was observed in two cases. This abnormality occurs with advanced hyperkalemia,[13] and this is probably the mechanism for the left bundle branch block pattern in Case 34, but the right bundle branch pattern observed in Case 35 cannot be explained on that basis, since the abnormality was noted before the hyperkalemic effect became apparent.

Electrocardiographic evidence of pericarditis as manifested by RS-T segment elevation was demonstrated in only one case (Case 47). This patient also had a pericardial friction rub and clinical and laboratory evidence of severe uremia.

The electrocardiograms were abnormal in six (Cases 4, 9, 22, 34, 43, and 44) of the seven fatal cases. A complete decription of each is provided in Table I. In brief, some evidence of hyperkalemic effect was noted in five cases. In two it was advanced; in two it was indicated by the abnormal appearance of the T waves, one of which also showed multiple auricular premature beats; and in one the T waves in some leads suggested hyperkalemic effect while in other leads there were nonspecific negative T-wave changes. The sixth case also showed inverted T waves and a prolonged Q-T interval and was the only case coming to autopsy showing any evidence of the myocarditis described by Hullinghorst and Steer.[7] The seventh fatal case was the only one in which the electrocardiogram was normal; however, only a single tracing was taken and this was recorded on the ninth day of illness, one day before the patient's death. The nonprotein nitrogen on that day was 130 mg. per cent. The urinary records are incomplete due to the fact that the patient was transported from Korea on the ninth day. He suffered from severe hemorrhagic phenomena, but no shock or other cardiovascular manifestations and died in a toxic delirious state.

At autopsy each of the seven fatal cases showed hyperemia and hemorrhage in the wall of the right auricle and scattered areas of petechial hemorrhage throughout the heart. The heart in only one case (Case 22) weighed more than 400 grams. Each of the six cases with abnormal electrocardiograms showed edema, hyperemia, and focal hemorrhage in the lungs. In three the pulmonary edema was severe (Cases 22, 43, and 44). The case in which the electrocardiogram was normal showed pulmonary hyperemia and focal hemorrhage but no edema. In addition, the characteristic hemorrhages of hemorrhagic fever[7] were noted in the pituitary, kidneys, stomach, bowel, pleura, peritoneum, and skin in variable degrees of severity. The typical "kidney of E. H. F."[7] was seen in all cases. Because of the multiplicity of serious features of this disease, it is difficult to ascribe an immediate cause of death in most of these cases. The most important findings from a cardiovascular standpoint are described in Table I, but it is likely that a combination of deleterious effects was involved in all cases.

*Electrocardiograms Recorded During the Convalescent Stage.*—In the second group of seventy-eight cases studied during the convalescent stage of illness, variations from normal were noted in seven patients. In this group, nineteen had had electrocardiograms taken during the acute phase of illness and eighteen of the nineteen are considered in that portion of the paper. Thirteen of the nineteen were abnormal at some time during the acute stage, but ten of these had returned to normal by the time of the convalescent tracing. Two of the remaining three cases (Cases 35 and 55) that continued to show abnormalities have been presented in the acute series. Case 35 continued to show the right bundle branch block, and Case 55 showed a persistence of nonspecific negative T-wave changes, without cardiovascular symptoms, long after the patient had subjectively recovered. Serial study in the latter case, however, demonstrated a definite progression towards normal, so that it appears probable that eventually all of the electrocardiographic abnormalities disappeared. The third case is the patient with auricular fibrillation who was not transferred to this hospital until late in convalesence. The abnormality was discovered on the fourth day of illness and except for the arrhythmia the course was mild and uneventful. There were no associated cardiovascular manifestations, and the ventricular rate was stabilized at about 80 beats per minute without medication. Shortly after admission to this hospital, 72 days after onset of illness, the patient was given two courses of quinidine sulfate with total doses of 2.6 and 3.0 Gm., respectively. However, neither was successful in producing a sinus mechanism, and the auricular fibrillation was still present 138 days after onset of illness when he was evacuated to the Zone of Interior.

Of the ten previously abnormal cases which had returned to normal by the time of the convalescent tracing, there were four instances of hyperkalemic effect (Cases 13, 19, 30, and 47), six of probable hyperkalemic effect (Cases 12, 18, 28, 37, 38, and 50), one of nonspecific negative T-wave change (Case 30), one of sinus bradycardia (Case 50), one of RS-T segment elevation (Case 47), and five of prolongation of the Q-T interval (Cases 13, 30, 37, 47, and 12). It should be noted that the diagnosis of "probable hyperkalemic effect" is based in part upon the return to normal of T waves which during the acute phase of the disease suggested hyperkalemic effect.

Four of the seven tracings that showed variations from normal during convalescence were not studied electrocardiographically during the acute stage. It is our impression that the changes in these tracings are slight and of questionable significance. The clinical course in all four was mild, with minimal hemorrhagic phenomena, mild azotemia and oliguria, and no cardiovascular manifestations. The first case showed prolongation of the P-R interval to 0.22, 0.25, and 0.24 second in three tracings recorded 71, 73, and 79 days, respectively, after onset of the illness. The second case showed elevation of the RS-T segment in the precordial leads to slightly above the upper limit of normal in two tracings recorded 39 and 59 days after onset of the illness. The third case showed variably flattened T waves in Leads II, $V_5$ and $V_6$, and slight asymmetrical inversions in Leads III and $aV_F$ in a vertical heart with forward rotation of the apex. Six tracings were

recorded from the twenty-ninth to the seventieth day of illness. In two of these the flattened T waves in Leads II, $V_5$ and $V_6$ were upright, but progression toward or away from normal was not demonstrated. The fourth case showed asymmetrical T-wave inversions in Leads $V_1$, $V_2$, $V_3$, and $V_4$ of decreasing depth proceeding from right to left across the precordium in a vertical heart with moderate clockwise rotation of the longitudinal axis and forward rotation of the apex in two tracings recorded 58 and 60 days after onset. The T waves in the last case probably represent persistence of the juvenile pattern since this patient was a Negro.[13] It is our opinion, therefore, that only two of the seven cases with electrocardiograms showing variations from normal during convalescence have abnormalities sufficient to suggest permanent cardiac damage from hemorrhagic fever. One of these cases was the patient with right bundle branch block and the other was the patient with auricular fibrillation. Even in these, since tracings were not taken before the abnormalities were discovered, it is impossible to be certain that they were the result of hemorrhagic fever.

## SUMMARY

1. One hundred forty-seven electrocardiograms from fifty-five cases of hemorrhagic fever taken during the acute stages of the disease and 90 electrocardiograms from seventy-eight cases in the convalescent stage of the disease have been reviewed and correlated with the significant clinical findings.

2. Abnormalities or suggestive abnormalities were noted in one or more tracings of twenty-seven of the fifty-five cases in the acute series.

(a). Hyperkalemic effect was the most common change noted, since its presence was indicated or suggested in seventeen cases. It was in general related in timing and frequency to the oliguria and resultant azotemia.

(b). Prolongation of the Q-T interval was noted in eleven cases during oliguria and in four during diuresis.

(c). Sinus bradycardia was noted in four cases and multiple auricular premature beats in one. The rarity of disturbed impulse formation is surprising in view of the almost constant auricular pathology at autopsy.

(d). Nonspecific negative T-wave abnormalities, usually mild and transitory, were noted in nine cases. A possible explanation for the relative infrequency of this finding is the influence of concomitant hyperkalemic effect in neutralizing tendencies to T-wave negativity.

(e). One case each of left and right bundle branch block was noted. The former was probably due to advanced hyperkalemic effect, but a satisfactory explanation is not available for the latter.

(f). One case of RS-T segment elevation due to uremic pericarditis was observed.

(g). Electrocardiograms were abnormal in six of the seven fatal cases. Five of the six cases with abnormal tracings showed some evidence of hyperkalemia. In two of these it was advanced. In one case there were multiple

auricular premature beats. In two cases there were nonspecific negative T-wave changes, one of which was the only case in the series in which myocarditis was demonstrated at autopsy. Despite the presence of gross right auricular hemorrhage in all cases, significant P-wave abnormalities were not observed.

3. Seven of the seventy-eight cases in the convalescent series showed variations from normal. In four of the seven, the changes were slight and of questionable significance. The other three include one case each of right bundle branch block, auricular fibrillation, and nonspecific but marked T-wave inversions. However, in the last case serial study revealed a definite progression towards normal. Therefore, only two cases in the series provide evidence that permanent electrocardiographic abnormality results from hemorrhagic fever. Even in these it is impossible to be certain that the abnormality did not antedate the illness. In addition, long term follow-up may reveal a return to normal.

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# THE HEART OF THE RAT* WITH SPECIAL REFERENCE TO THE CONDUCTING SYSTEM

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SINCE early times a great deal of attention has been paid to the general structure and histology of the mammalian heart. In 1893 Kent[6] noted the presence of muscular connections between atria and ventricles in the hearts of various mammals and stated that the heart of mammals does not differ from that of lower vertebrates (fish, amphibia, and reptilia) in the muscular continuity between the atria and the ventricles. Davies[2a] also observed the muscular connections of Kent in the hearts of birds and believed that the atrioventricular connections of the avian heart presented an arrangement which is intermediate between that of fish and reptile on the one hand and that of the mammal on the other. It is surprising that Davies with Francis[3a] contradicting his previous statement mentioned that the atrioventricular conducting (connecting) tissue of the hearts of birds and mammals is a neomorphic development and not a remnant of more extensive tissues of similar structure in the lower vertebrate heart. These observations are decidedly in disagreement with those of Kent,[6] but Davies and Francis[3a] did not refer to him either in the text or in the bibliography. Such an omission deserves serious consideration. More recently, Kistin[7] paid particular attention to the atrioventricular connections of the human heart. In the few hearts he studied, the bundle of His was the only connection between the atria and the ventricles, and he could not find the accessory muscular connections of Kent. He emphasized the need for further investigation.

In the present paper the minute anatomy of the heart of the rat, *Rattus rattus rufecens*, is described. The nature of the tissue present between the different chambers of the heart has been studied and particular reference has been made to the structures presumably associated with the initiation, control, and conduction of the cardiac stimulus for contraction.

## MATERIAL AND METHODS

The hearts were removed from chloroformed specimens of newborn rats and fixed in Bouin's picroformal. Serial transverse and longitudinal sections were cut by the paraffin-embedding process. The sections were 8 microns thick and were stained with acid fuchsin. Six complete series of such sections of the whole heart were obtained and examined.

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Zoology Department, Government College, Ajmer, India, Contribution No. 6.

Received for publication July 23, 1953.

*Rattus rattus rufecens, Gray.

## OBSERVATIONS

The heart shows the general topography of the mammalian heart in having two atria and two ventricles. The sinus venosus is, however, not distinctly marked outwardly.

*Sinus Venosus.*—It is a small thin-walled chamber closely applied to the dorsal wall of the right atrium and extending a little toward the cephalic and the dorsal sides of both the atria. The disposition of the sinus venosus over the atria is transverse with its anterior apex slightly tilted dorsally in a conspicuous manner. The sections passing through the sinuatrial region show that the sinus venosus is driven on its caudal side into the cavity of the right atrium (Fig. 1). The portion

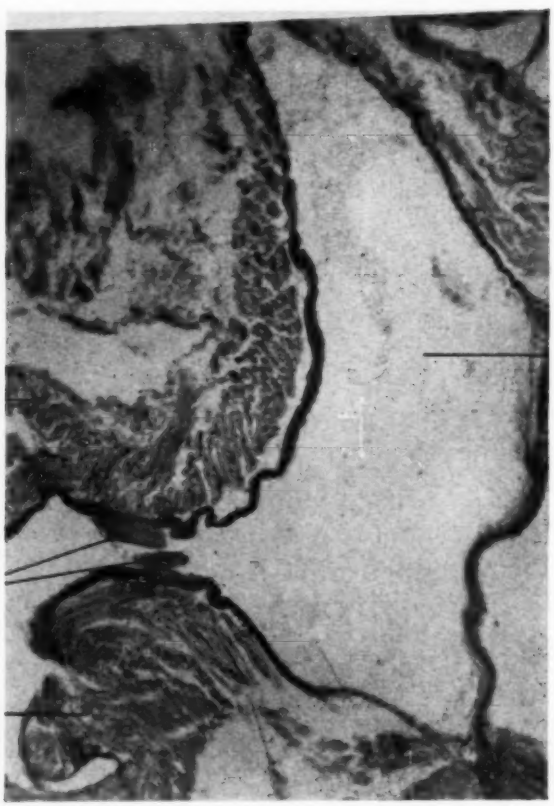


**Fig. 1.—Photomicrograph of the longitudinal section passing through the sinuatrial region. *R.A.*, right atrium; *S.A.V.*, sinuatrial valve; *S.V.*, sinus venosus.**

of the sinus lying inside the right atrium is much larger than the portion remaining out. Such an extension of the sinus venosus into the right atrium suggests that the former chamber is in the process of being incorporated into the latter, a condition achieved in many birds and mammals. The right duct of Cuvier runs almost dorsally and at right angles to the mid-longitudinal axis of the heart and opens into the sinus venosus dorsolaterally on the right side. This opening of the

right duct of Cuvier is dorsal to that of the left duct of Cuvier which opens by piercing the left lateral wall of the sinus venosus.

Because of the extension of the sinus venosus into the right atrium, the sinuatrial opening is situated within the right atrium. The sinus venosus, near the opening into the right atrium, becomes narrow and constricted to form a sinuatrial canal. This canal lies inside the right atrium and communicates with the latter's cavity through the sinuatrial opening which is guarded by two prominent rectangular padlike sinuatrial valves. These valves are formed of the sinus musculature and lie on the inner surface of its walls. Such a structure of the valves is fundamentally different from the valve structure of reptiles and birds[1] where a bilaminar type of sinuatrial valves is observed. As the sinus muscle fibers are continuous with the atrial muscle fibers, they afford the necessary muscular pathway between the sinus venosus and the right atrium for the transmission of the stimulus of contraction. The nature and the disposition of the sinuatrial valves, especially when they lie surrounded by atrial fibers, throw light on a new physiological aspect of the heart. When the sinus venosus contracts, the blood from this chamber flows through the sinuatrial canal into the right atrium. Because of the pressure of the blood flowing through the sinuatrial canal into the right atrium, the two sinuatrial valves get separated leaving a passage between them. As the valves are separated they also push back the neighboring atrial muscle fibers, and this results in the expansion of the right atrium to receive more blood from the sinus venosus.

*Atria.*—The two atria, the right and the left, hang freely on the two sides of the ventricles. They are triangular leaflike structures, broad in the middle and pointed at the two ends. The interatrial septum is small, thick, and muscular. The right atrium is larger and more spacious.

*Atrioventricular Junctions.*—As the ventricles are divided completely by the septum ventriculorum, the right and the left atria open through separate atrioventricular openings into the right and the left ventricles, respectively. Both the openings are guarded by valves, the valves of the right side being placed more dorsally than those of the left side. Both the right and the left atrioventricular valves are fibrous cellular structures entering deep into the ventricular lumen. The valves are elongated leaflike structures having many nucleated cells. The atrioventricular junctions are further characterized by the presence of special conducting and controlling structures, the atrioventricular node (Node of Tawara) and the atrioventricular bundle (Bundle of His).

*Atrioventricular node*: As in birds[1] the cephalic portion of the left ventricle is continuous with the caudal portion of the septal wall of the right atrium. It is in this region that the atrioventricular node is situated. The node is oval in shape (Figs. 3A and 3B) and lies slightly tilted toward the right atrioventricular orifice. It has a thick sheath of muscle fibers all around it. The node consists of a number of loosely arranged interlacing muscle fibers. Numerous rounded nuclei are present inside the node.

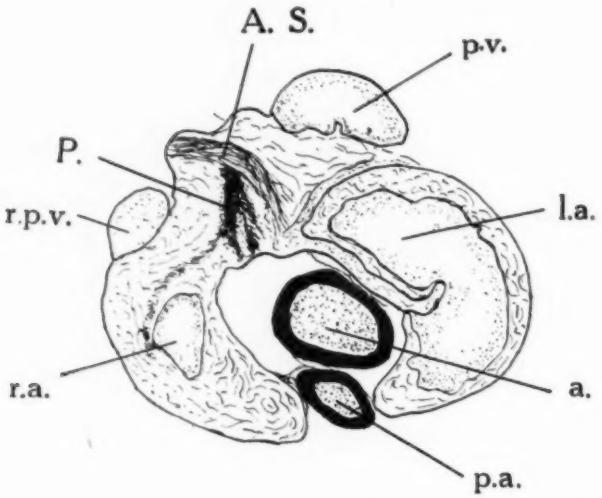


Fig. 2A.—Diagram to show the position of the Purkinje fibers at the interatrial septum. *A.S.*, atrial septum; *P.V.*, pulmonary vein; *L.A.*, left atrium; *A*, aortic arch; *P.A.*, pulmonary artery; *R.A.*, right atrium; *R.P.V.*, right precaval vein; *P.*, Purkinje fibers.

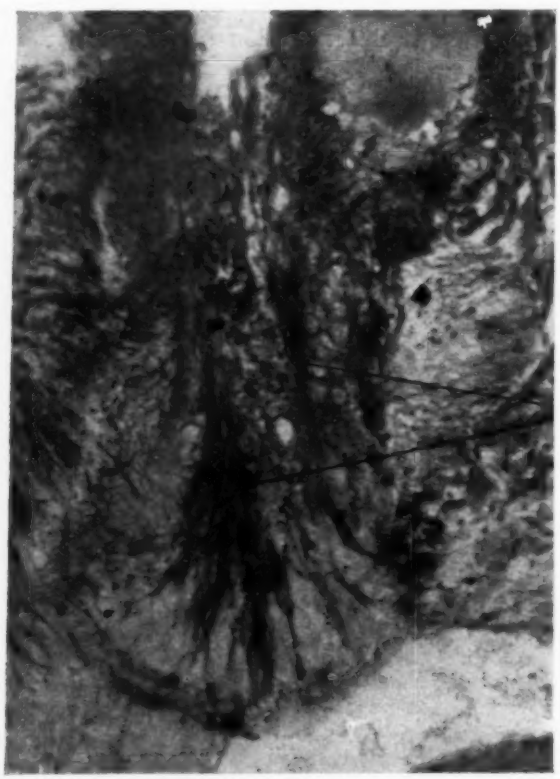


Fig. 2B.—Photomicrograph of the section to show the structure and distribution of Purkinje fibers. *P.*, Purkinje fibers.

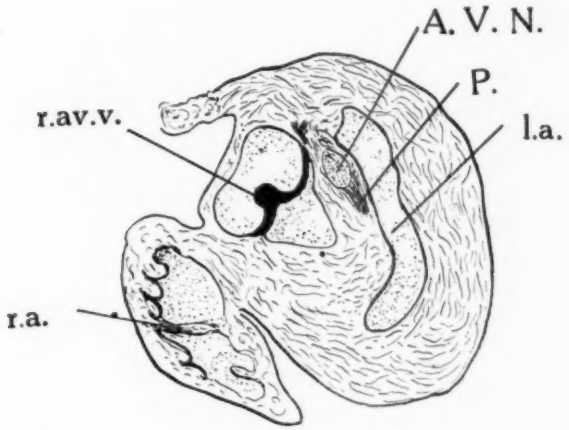


Fig. 3A.—Diagram to show the topographical position of the atrioventricular node. *A.V.N.* atrioventricular node; *P.*, Purkinje fibers; *L.A.*, left atrium; *R.A.*, right atrium; *R.A.V.V.*, right atrioventricular valve.

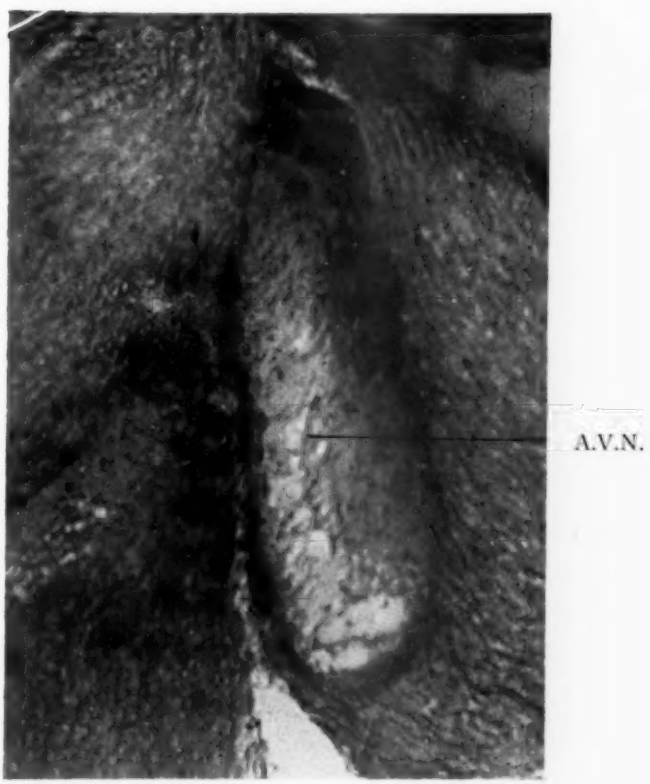


Fig. 3B.—Photomicrograph of the section through the atrioventricular node. *A.V.N.*, atrioventricular node.

*Atrioventricular bundle*: The atrioventricular bundle or the bundle of His is a well-defined, funnel-shaped structure lying in the upper portion of the interventricular septum (Fig. 4A). The transverse and longitudinal sections through this bundle show the presence of special fibers with nuclei (Fig. 4B). A thick broad circular rim forms the cephalic part of the bundle. The fibers are attached to this rim at regular gaps. The fibers of the bundle run anteroposteriorly, and after traversing the entire length of the bundle, converge in the posterior region to form the beak of the funnel-shaped bundle.

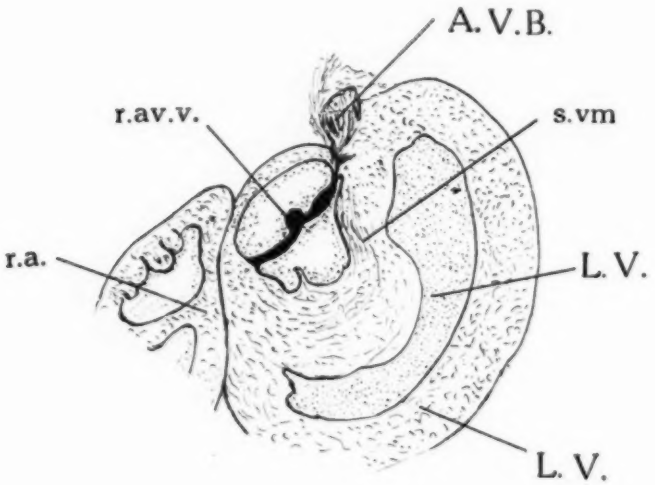


Fig. 4A.—Diagram to show the position of the bundle of His. *A.V.B.*, atrioventricular bundle; *S.Vm.*, septum ventriculorum; *L.V.*, left ventricle; *R.A.*, right atrium; *R.A.V.V.*, right atrioventricular valve.

The bundle bifurcates caudally into a right and a left limb. The right limb is very short and extends as a thick bandlike structure which runs for a short distance towards the tricuspid valve. The left limb goes further, deep into the muscle fibers of the interventricular septum and ramifies over its entire surface (Fig 4C). This limb has large Purkinje fibers containing cells with large rounded nuclei.

*Purkinje Fibers.*—An important feature of the atria is their well-knitted system of Purkinje fibers. These fibers are similar to those described in the atrioventricular node and the bundle of His. Their microscopic structure[7] is quite different from that of the other cardiac fibers. These structures are larger, have prominent, deeply stained nuclei and take a very deep stain with acid fuchsin. The individual Purkinje fiber may have either a single nucleus or more than one, but in some sections only vacuolated cytoplasm is seen. These fibers are very closely packed together beneath the atrial endocardial lining, and the atrial cavity is bridged over transversely by them. The interatrial septum is also

Fig. 4B.—Photomicrograph of a section through the bundle of His to show its histological structure. *R.A.V.V.*, right atrioventricular valve; *A.V.B.*, atrioventricular bundle.

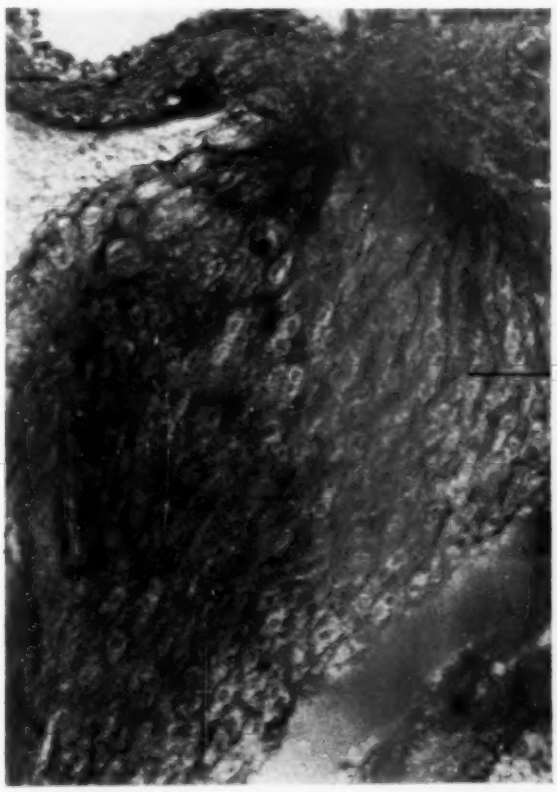


Fig. 4C.—Photomicrograph of the section passing through the left limb of the bundle of His. *R.A.V.V.*, right atrioventricular valve; *L.B.*, left limb of the bundle of His.

very richly supplied with Purkinje fibers. These fibers, at the septum, are arranged in longitudinal strands and branch profusely on either side (Figs. 2A and 2B). They extend into the bases of the atrioventricular valves but do not continue any further down. Thus, even the Purkinje fibers which together with the bundle of His are part of the single atrioventricular system[10] do not enter and are not continuous with the ventricular fibers. The necessary muscular continuity between the atria and the ventricles is established only through the bundle of His. A search for the scattered atrioventricular connections of Kent[6] was thoroughly made. For this, the hearts of six newborn rats (because according to Kent muscular connections are more numerous in young than in adult specimens) were taken. In each case serial sections were prepared of the whole heart and every section of the series was examined. This study confirms the absence of multiple atrioventricular muscular connection in the hearts of rats.

## DISCUSSION

So far two differing theories have been put forward to explain the conduction and control of the cardiac impulses passing from one chamber of the heart to the other. The myogenic theory states that the conducting tissue is muscular in nature. The neurogenic theory postulates the presence of nerve elements to account for the initiation, control, and conduction of the cardiac rhythm. Recent workers[1-3,5] however, are unanimous in stating that there is a specialized muscular connecting tissue in the hearts of birds and mammals for the propagation of these impulses. The present investigation has revealed that the structures shown to be responsible for the initiation, control, and conduction of the cardiac stimulus in rat are muscular in nature, and therefore this affords additional evidence in favor of the myogenic theory of cardiac conduction.

Kent[6] pointed out that muscular continuity exists between the atria and the ventricles in the heart of newly born rats. However, he observed, instead of a single atrioventricular connection (through the bundle of His), that numerous muscle fibers connect the atria to the ventricles. According to him the fibers sweep uninterruptedly through from atrium to ventricle.

This study of the hearts of newborn rats was made to verify Kent's observations. It has been seen that no other connection except that through the bundle of His exists between atria and ventricles. The atrial muscle fibers do not enter into the ventricular cavity and are also not continuous with the fibers of the ventricular wall or with those of the interventricular septum. Moreover, the atrial Purkinje fibers also extend only to the base of the atrioventricular valves. It is only through the fibers of the bundle of His that a continuity is established between the atria and the ventricles for the propagation of the cardiac stimulus.

It is true that the atrioventricular connections of Kent have been observed in birds,[2a] but there they probably act as accessory pathways, in addition to the bundle of His, for a quick transmission of the impulse from atria to ventricles which is essential in these animals correlated with their rapid rate of the heart beat. In the human hearts which do not beat so fast, the presence of accessory connections is not necessary. Thus, as far as the proper functioning of the mam-

malian heart is concerned, the absence of accessory muscular connections can easily be explained.

When the impulses are being conveyed from the atria to the ventricles, they are temporarily delayed at the atrioventricular groove. This delay is necessary in order to allow the ventricle to be filled completely with blood before it in turn begins to contract. The peculiar structure and disposition of the bundle of His clearly illustrates the cause of this delay in the passage of the impulse. The bundle is a funnel-shaped structure, and as its wide cephalic portion occupies the total junctional area between the atria and the ventricles, the contraction wave coming from the former chamber to the latter must be picked up by it. The longitudinally arranged numerous fibers of the bundle carry the impulse from its cephalic to the much narrower caudal end where all these fibers converge to form the beak of the funnel-shaped bundle. As the number of the fibers of the bundle is large, the impulse may take a fairly long time to pass through their entire length. The caudal end being narrow will offer enough resistance to cause delay in an early transmission of the impulses to ventricles. On the contrary the multiple atrioventricular connections of Kent will transmit the impulse very quickly through the atrioventricular groove and this will disturb the coordination in the contraction movements of the atria and the ventricles. Referring to the "pause", Kent[6] stated that in newly born animals a large number of undifferentiated fibers pass from atria to ventricles and therefore in them the time taken by the contraction wave to pass over the atrioventricular groove is short while in older animals where the number of fibers is less and differentiation of fibers has taken place the time taken is longer. Kent evidently meant that the 'pause' or the delay in the passage of the contraction wave is peculiar to the hearts of adult animals only. However, he has not given any reasons to support his views. This omission deserves consideration. The delay or the 'pause' is necessary in adults, as well as in young animals, and it is also true that without postulating the presence of an atrioventricular bundle or any other such structure it will be rather difficult to account for it.

Kent[6] showed that the mammalian heart does not differ from that of cold-blooded animals in having a break of the muscular continuity between atria and ventricles. Prakash[9] has shown that this break in the muscular continuity of the cardiac chambers is not only peculiar to mammals but also occurs in the heart of lower vertebrates. An atrioventricular plug which is present at the atrioventricular junction of the heart of *Heteropneustis fossilis* corresponds structurally and functionally to the 'bundle of His' and is the only connection between the atria and the ventricle. In the light of these findings Kent's conclusions, however, can easily be questioned.

Davies[2c] in a lecture at the Royal College of Surgeons, London, remarked that "the comparative anatomy of the conducting system of the vertebrate heart reveals that the phylogenetic evolution of the system affords a further illustration of the dictum on the close correlation between form and function enunciated by John Hunter". During the course of the same Lecture he concluded on the basis of the above law that the conducting system of the bird's heart is far

better developed than that of the mammalian heart. Though full agreement with the law of John Hunter as elucidated by Davies can be made some doubts are raised as to the general conclusion arrived at by Davies. On comparing the results of the present investigation on the heart of the rat with those of Adams[1] and Davies[2] on birds, it is clear that the system of Purkinje fibers, the atrioventricular node and the bundle of His, are all more extensive and well developed in the rat than in birds. An extensive ramification of Purkinje fibers in both the atria and also at the atrial septum is a unique feature of the heart of the rat and has so far not been observed in any bird. As Davies[3b] himself interpreted that these fibers form a part of the special conducting tissue, the efficiency of the heart of the rat in the control and conduction of the wave of excitation can not be underestimated.

It is true that the sinuatrial node (Keith-Flack's node)[5] the 'pacemaker' or the site of the initiation of the cardiac impulse is absent in the rat. It can not be concluded because of the absence of the node only that the conducting system of the heart of all the mammals is less efficient than that of birds, particularly when this node is also absent in many birds.[1]

The sinuatrial node is generally present in all those birds[2] and mammals[3b] where the sinus venosus is absent or greatly reduced. This node is, however, absent in those birds[1] where the sinus venosus is well developed. These facts point out that the sinuatrial node develops, in the heart of vertebrates, in relation with and consequent to the reduction of sinus venosus. Therefore, the presence or otherwise of this node in some individual birds or mammals is no criterion in judging or comparing the efficiency of the heart of different vertebrates.

## SUMMARY

1. The sinuatrial node is absent in the rat. It develops in relation with and consequent to the reduction of the sinus venosus.

2. The sinuatrial valves are rectangular padlike structures. They enter deep into the cavity of the right atrium. The continuity between the atrial and the sinus muscle fibers offers the necessary muscular pathway for the transmission of the wave of contraction from the sinus venosus to the atria.

3. An extensive distribution of Purkinje fibers has been observed and described in the atria and at the interatrial septum of the heart of the rat.

4. The atrioventricular node is present at the junction of the cephalic portion of the ventricle and the caudal part of the septal wall of the right atrium. Such a position of the node corresponds with that of birds.[1]

5. The muscular atrioventricular bundle is a funnel-shaped structure and is the only connecting tissue between the atria and the ventricles.

6. It has been argued that the structures associated with the control and conduction of the cardiac rhythm in the heart of the rat are not less efficient than those in the hearts of birds.

I am specially indebted to Dr. P. N. Mathur for his keen interest and guidance and to Principal V. V. John for providing me with the necessary facilities in connection with this work. I wish to thank Dr. Albert D. Kistin, Washington, D. C., for reviewing the manuscript.

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# PERFORMANCE OF ANGIOCARDIOGRAPHY AND CARDIAC CATHETERIZATION AS A COMBINED PROCEDURE*

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IN MOST, if not all, cases requiring cardiac catheterization, angiocardiography will contribute additional information germane to both diagnosis and management. Thus it is often desirable to perform both procedures as a part of the same examination. In the last twenty-five cases this has been entirely practicable and without hazard to the patient. By the method to be described a considerable saving in time, personnel, and equipment has resulted, and satisfactory visualization of the left heart and aorta has been regularly obtained. Angiocardiography is first performed and if the results are inconclusive, catheterization is accomplished.

## METHOD

Following the lead of Chavez and associates[1] in Mexico, and Sutton and associates[2] in this country, an effort was made to perform angiocardiography through the right external jugular vein. This was generally unsatisfactory in our hands. In addition to the technical difficulty of directing the flexible rubber catheter around the angular bend between the external jugular vein and the superior vena cava, significant hazards of contamination were encountered in positioning the patient for injection. These were especially prominent in the anesthetized child. However, it was clear that films of superior diagnostic quality were obtained by this method (Fig. 1).

Because of the foregoing advantages and disadvantages, we have used the basilic vein in the upper third of the arm in children and adults and the femoral vein in infants. They afford ample channels which permit passage of a large catheter for injection of the dye close to the heart and the scar site is ideal. A particular additional advantage lies in the requirement of less dye. Ordinarily a period of 1 to 2 sec. is required for the dye to pass from the anticubital vein and opacify the right side of the heart. During this time, it is undergoing continual dilution. By introduction of the dye through the catheter and close to the heart, thus avoiding this dilution, the adult dose used for satisfactory visualization

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Received for publication Aug. 24, 1953.

*Dr. George R. Herrmann, Professor of Medicine, University of Texas, and Consulting Cardiologist to Brooke Army Hospital, has advised in the diagnosis and management of cases reported. Their presentation would not have been possible without the benefit of his professional guidance, personal interest, and encouragement.

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has been reduced by an average of 20 per cent. In addition, the patient is tilted upward at a twelve-degree angle. This assures many of the advantages of rapid heart filling in the upright-seated patient without requiring his active cooperation (Fig. 2,A).

The same vein is used later for cardiac catheterization. Insertion of a cardiac catheter (size 8F to 9F) at this high level possesses two further advantages: (1) Shortening the distance from tip of the catheter to the guiding hand of the examiner facilitates its manipulation; (2) use of a shorter and larger catheter lessens artifacts in recorded pressures.[3]

## PROCEDURE

Although inpatient status is preferred, the method has been applied equally well to outpatients. Premedication consists of a barbiturate, Demerol, and quinidine with dosage adjusted for age and weight. Light general anesthesia with local infiltration is used for infants and small children. The patient is placed on roentgenographic table with his head opposite to that end of the table where catheterization is to be performed. Under local anesthesia and with a high venous tourniquet in place, a 3 cm. incision is made on the medial side of the arm slightly proximal to the junction of the middle and upper one-third and a 3 cm. segment of the basilic vein is exposed. It lies directly under the deep fascia, medial to the coraco-brachialis muscle and adjacent to the median nerve. The vein is collapsed by the spring tension of a tissue forceps placed under it and precautionary untied ligatures are inserted under the vein at both ends of the exposure. A side of the vein is then opened with a tissue scissors and an obliquely cut polyethylene tube is inserted. We have routinely used a standard polyethylene medical tubing with an internal diameter of 0.106 inch and an outside diameter of 0.138 inch. This is of such size that it fits snugly over the outside of a Robb-Steinberg needle and syringe[4] which are used for injection. The length of tube used is cut so that full insertion will carry its tip well into the vena cava. During its passage, if deterrent spasm is encountered, a hot water bottle under the arm is helpful. If more venous relaxation is needed, Hexamethonium Bromide has seemed to promote venous relaxation as described by Restall and Smirk;[5] doses of 3 to 10 mg. have been used. (Morphine used for premedication significantly increases venous spasm.) Rotating the catheter is helpful in its insertion as is the application of procaine to the outside of the vein. Although placement of the catheter is performed blindly, its precut length limits the extent of insertion. During passage of the tube and before and after the actual injections of dye, a slow intravenous drip of 5 per cent glucose with 100 mg. heparin per liter is maintained through the catheter by means of a three-way stopcock. When the tube is fully inserted, the incision is packed, covered with an elastic bandage, and sterile technique discontinued. At this time, under fluoroscopy a test dose of 2 c.c. of dye is slowly injected which serves to opacify the radioluscent catheter. If it has ascended into the neck it is repositioned by withdrawing it as far as the junction of the subclavian vein and superior vena cava. At this point the patient receives an additional 10 to 75 mg. of Demerol through the venous catheter and oxygen by mask. He is then positioned on the tilted changer (Fig. 2A), and the injection is made

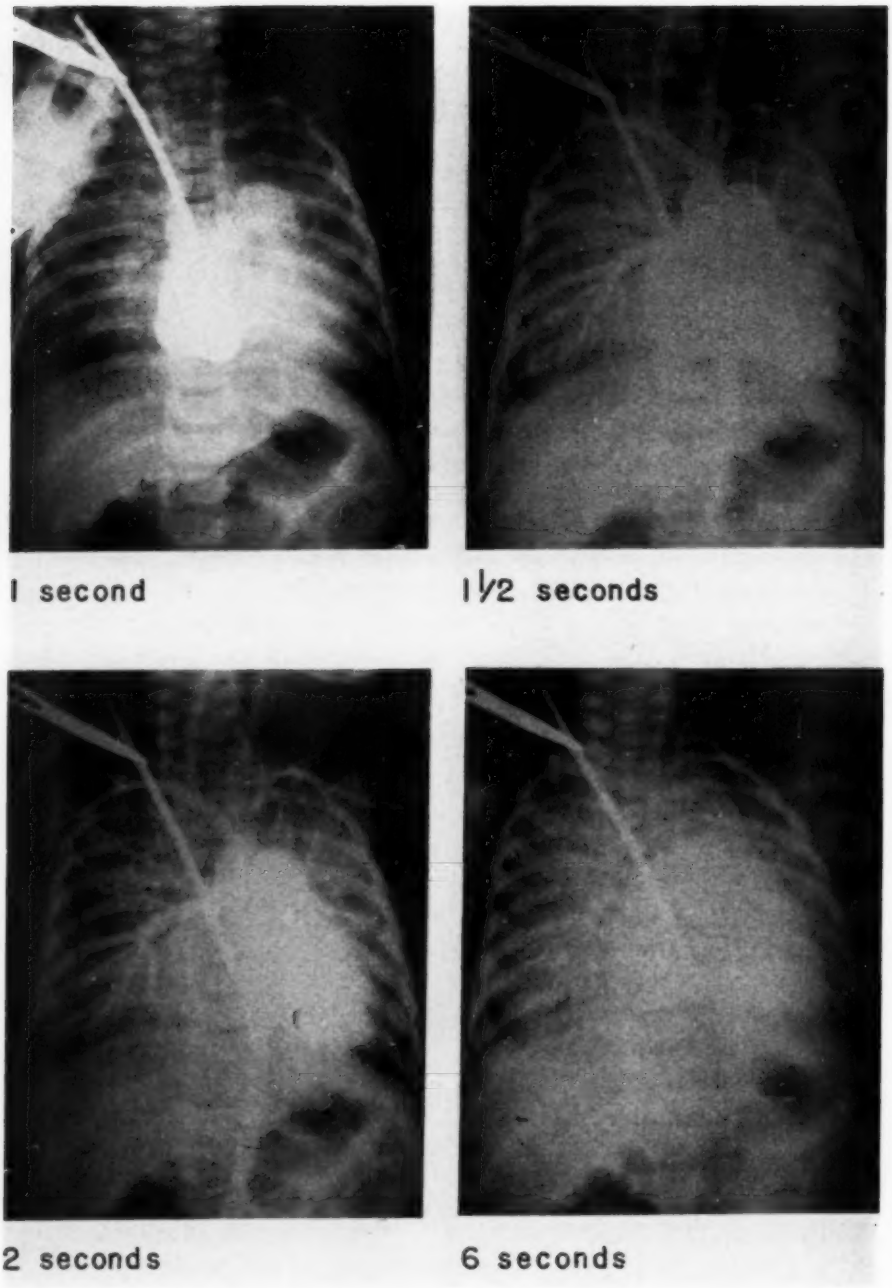


Fig. 1.—Atrial septal defect with overriding aorta: (mitral atresia). Extreme degree of dextroposition of overriding aorta was indicated by filling of abdominal arterial trunks at 1½ sec. Note apparent inability of dye to leave the pulmonary circulation after aorta was no longer clearly seen (Case 1). Roentgenographic reproductions by Photographic Section, Brooke Army Hospital, Br. Neg. No. 11516.

Fig. 2.—A, Method of obtaining gravity inflow to the heart without requiring volitional cooperation of the patient. X-ray tube's perpendicular alignment with camera's grid is assured by physically opposing tube cone and camera before patient is positioned.

B, Device used for auditory monitoring of heart rhythm during cardiac catheterization. Small microphone is placed in patient's axilla. When extrasystoles are heard, their electrocardiographic form may be seen on a cathode-ray oscilloscope with a persisting-image type of screen (not shown).

without reference to the patient's cooperation in taking a deep breath. First exposure is made as the injection is started. Fourteen or sixteen films are made at 1/2 sec. intervals with the exposure factors of 500 Ma, 1/15 sec., 90 kv., and 36-inch distance for the average adult in the axiopulpal position. Kilovoltage and time are reduced in children but not proportionately so; 70 kv. has been minimal.

In infants less than one year of age the catheter has been inserted through the femoral vein. The patient is tilted in the reverse position to that described above. The amount of dye used has been 1 c. c. per pound up to body weights of 15 pounds. This is considerably less than recommended by Kreutzer and associates.[6]

When exposures are satisfactorily completed, usually in two planes, the patient is reversed on the roentgenographic table, the polyethylene catheter replaced with the cardiac catheter, and the catheterization performed under fluoroscopic control with the assistance of a radiologist.

By the innovations noted next, the team required for cardiac catheterization has been reduced to the cardiologist, radiologist, and two technicians. These innovations are essentially two in number: (1) Outlets from Twin-Viso Recorder are connected to a cathode-ray oscilloscope with a P-7 screen (persistent image screen).* This permits the operator to view either the patient's electrocardiogram or intracardiac pressure pulse during the procedure. (2) Audioamplifier and loudspeaker attached to a small microphone in patient's axilla enable the operator to hear extrasystoles and at the same time see their form on the oscilloscope screen.† One means of auditory monitoring of rate and rhythm during catheterization is achieved by the use of the Stethetron electric stethoscope: to the output opening for the ear piece is applied a second crystal microphone which is attached to any conventional amplifier system such as radio, record player, tape recorder, etc., (Fig. 2,B). The "double pickup" provides sufficient volume to be adjustable within a wide range. Although tonal quality is deficient, extrasystoles can be recognized as readily as with the conventional stethoscope. At the same time electrocardiogram and pressure curves may be recorded as desired.

Other details of catherization are as established at this hospital by Colonel Richard P. Johnson, Medical Corps.[7] Particular emphasis is placed on the collection of three blood specimens from each heart chamber and major vessel for the determination of average oxygen saturations. Oxygen saturation is closely approximated during catheterization with the Waters-Conley Oximeter and subsequently determined by photometric laboratory analysis modified after the method‡ of Hickam and Frayser.[8]

## CASE REPORT

CASE 1.—K. P., 4-month-old infant with distended superficial veins had been cyanotic since birth. There was no clubbing; hemoglobin was 15 Gm.; weight, 7 pounds and 7 ounces. A continuous murmur was heard over the protuberant upper left chest. The electrical axis of electrocardiogram was plus 130 degrees. Peripheral arterial oxygen saturation averaged 75 per cent;

*Cambridge Educational Cardioscope has been available at this hospital. Other oscilloscopes are satisfactory.

†Suggested by Captain James Ewart, Medical Corps, Brooke Army Hospital.

‡Analytical laboratory procedures by Fourth Army Area Medical Laboratory.

jugular blood, 68 per cent. Blood from the right atrium was 86 per cent saturated. Angiocardiogram (Fig. 1) indicates simultaneous filling of the aorta and pulmonary arteries together with continued recirculation of the dye in the lungs after the aorta is no longer visualized. Combined findings suggested the diagnosis of mitral atresia with extreme overriding of the aorta and atrial septal defect. Anatomic examination three months later showed hypoplasia of the ascending aorta and mitral valve, 3 cm. atrial septal defect, extreme overriding of the aorta and bronchopneumonia. The ductus was closed.*

Aortic hypoplasia was felt insufficient to classify this case within the diagnostic category of aortic atresia as defined by Taussig.[9]

CASE 2.—R. S., 8-year-old white boy with 5-year clinical diagnosis of coarctation, developed leg pain with exercise. There were no arterial pulsations in the lower extremities. Rib notching was observed. Blood pressure in the arms had gradually risen from 90/60 to 140/80 mm. Hg. Prominent scapular arterial pulsations were present, and there was a widely transmitted Grade 4 aortic systolic murmur and thrill. Angiocardiogram (Fig. 3) demonstrates a localized constriction of the aorta at the anatomic site of the ligamentum arteriosum.†

CASE 3.—E. S., 170 pound, 16-year-old girl with characteristic moon face[6] had been hospitalized four times during the preceding four years because of episodes of tachycardia and associated congestive failure with cyanosis. An electrocardiogram showed right ventricular hypertrophy. The pulmonary artery was dilated without hilar pulsations. The additional findings of a Grade 5 systolic murmur and thrill maximal in first left intercostal space and a faint $P_2$ suggested the clinical diagnosis of pure pulmonic stenosis as emphasized by Blount and associates.[11] Cardiac catheterization demonstrated a right ventricular systolic pressure of 75 mm. Hg and a pulmonary artery pressure of 25 mm. Hg. Oxygen saturation was normal. Angiocardiogram (Fig. 4) showed the stenosis to be valvular with post stenotic dilatation and further indicated an absence of intracardiac shunt as reflected by fading of the pulmonary artery before visualization of the aorta. Pulmonary valvulotomy was recommended and successfully performed with marked increase in exercise tolerance.

CASE 4.—R. E., 5-year-old boy, cyanotic from birth, showed no increase in cyanosis with exercise. There was no history of squatting. Growth retardation was prominent. Hemoglobin was 20 Gm. Resting oxygen saturations averaged 60 per cent; after exercise, prolonged standing and squatting, there was no change. An electrocardiogram showed electrical axis of plus 160 degrees. Grade 5 roaring murmur was limited to systole, and there was a loud pure $P_2$. Cardiac silhouette suggested tetralogy of Fallot. Cardiothoracic ratio was 50 per cent.

At catheterization, right ventricular pressure was 100 mm. Hg and oxygen saturation averaged 55 per cent. In the aorta, to which the catheter readily passed the oxygen saturation was 60 per cent and blood pressure the same as in the right ventricle. Catheter also passed from right atrium through an atrial defect into the left atrium where oxygen saturation was 93 per cent. Pulmonary arterial blood could not be sampled. Angiocardiography (Fig. 5) showed extreme dextroposition of the aorta and pulmonic stenosis. Filling of the pulmonary artery before the left ventricle excluded transposition of the pulmonary artery. Truncus and pseudo truncus arteriosus were excluded by finding blood of higher oxygen saturation in the aorta than in the right ventricle. Findings were confirmed at surgery,‡ and peripheral arterial oxygen saturations rose to 80 per cent after performance of a Blalock-Taussig operation. Better result was not expected because of the degree of dextroposition of aorta.

CASE 5.—M. M., 26-year-old woman had been cyanotic since birth and her activity had been seriously restricted by dyspnea. Hemoglobin, 17 Gm. The heart was not significantly enlarged and there was right ventricular hypertrophy by electrocardiogram. Widely transmitted Grade 5 systolic

*Post-mortem examination performed by Captain Michael H. Sulak, Medical Corps.

†Major Samuel F. Crabtree, Medical Corps, of the X-ray Service has materially contributed to the success of the angiocardiographic studies described by his attention to radiological techniques and by his personal interest and ability in diagnostic evaluation.

‡Surgery in these cases has been performed by Dr. Denton Cooley, Cardiovascular Surgical Consultant of Houston, Texas, and Col. Warner Bowers, Chief of Surgical Service, Brooke Army Hospital.

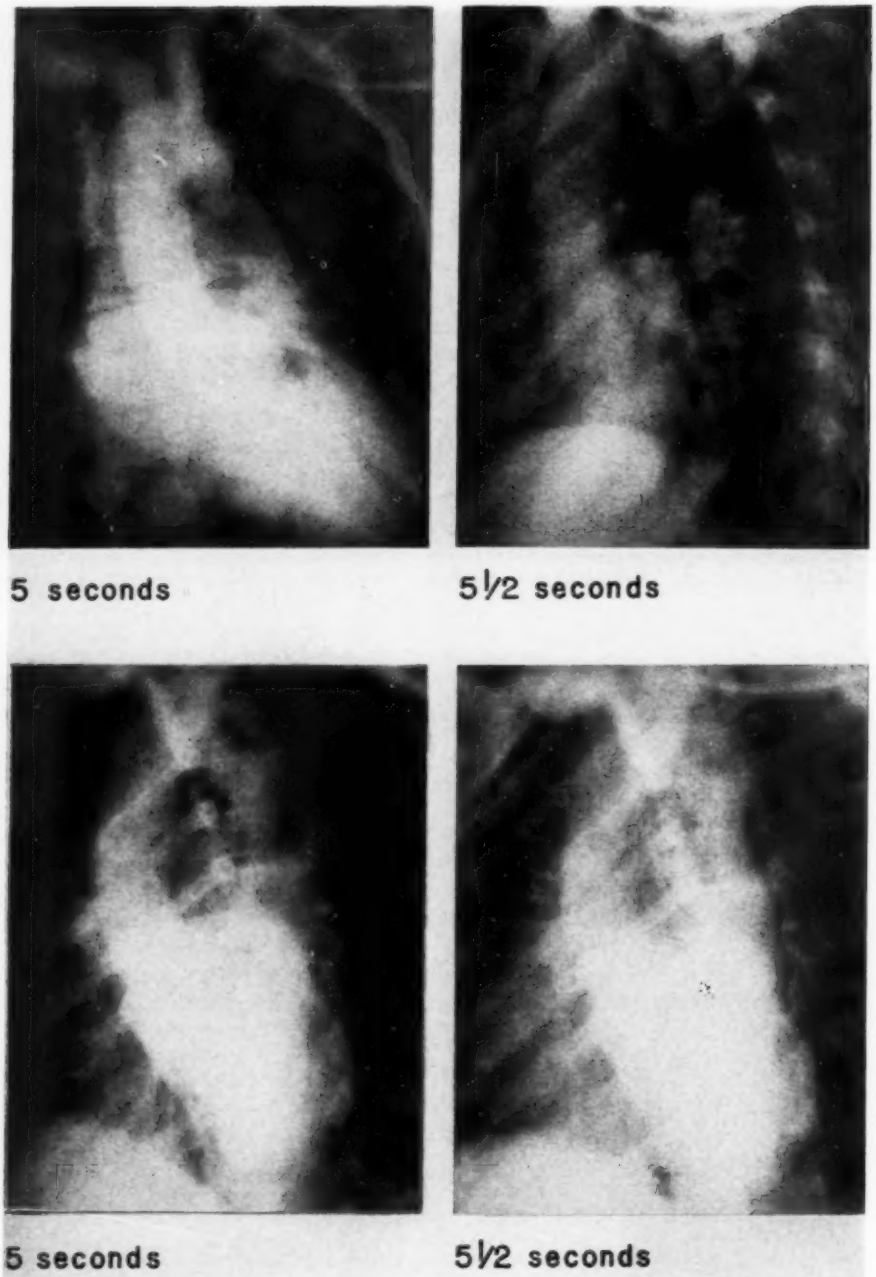


Fig. 3.—Coarctation: Films in three positions showed site and localization of constriction as well as normalcy of aorta below. A large collateral ran parallel to the coarcted segment. Collateral filling in aortograms may obscure definition of defect. Note outline of left atrium which overlies the aorta. Injection was made into superior vena cava (Case 2). All roentgenograms, negatives, and photos are unretouched.

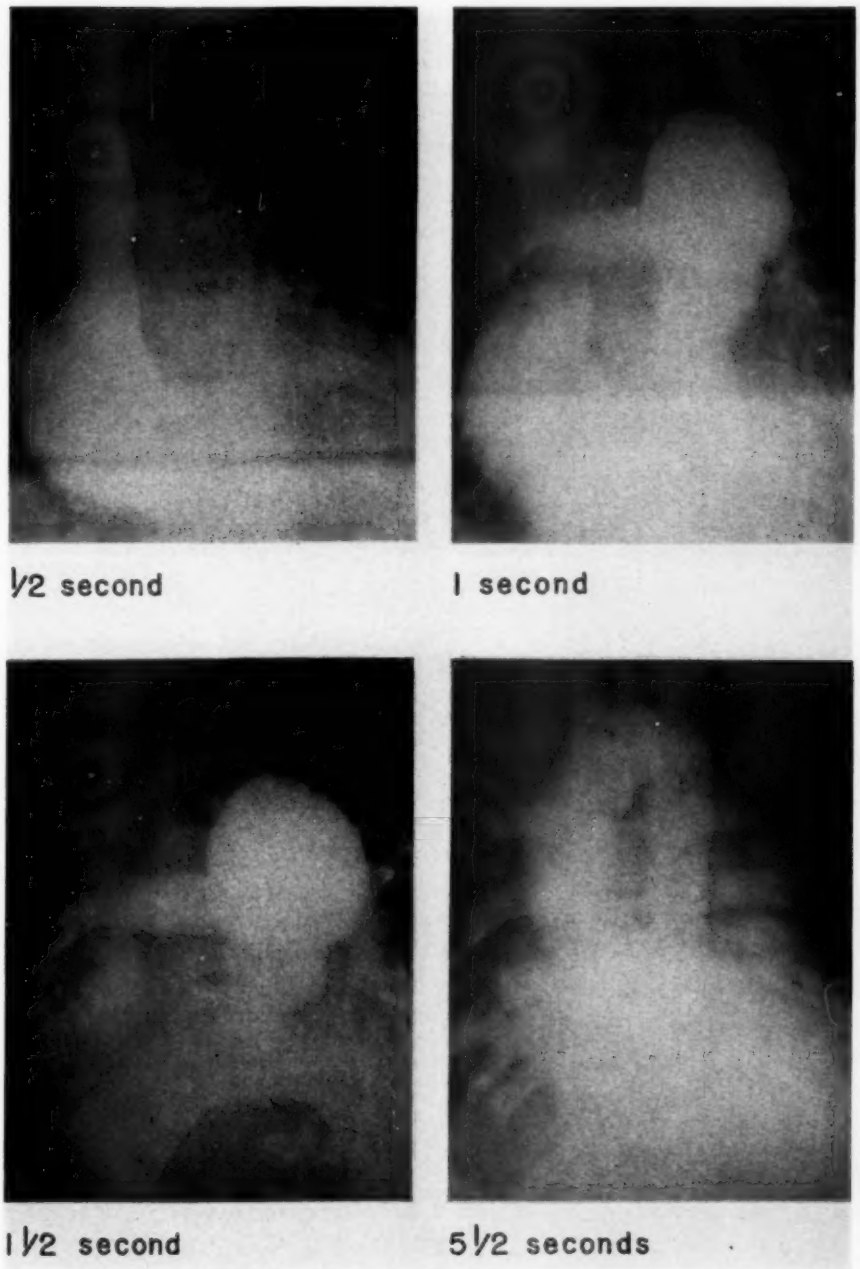


Fig. 4.—Isolated pulmonic stenosis: Large poststenotic dilatation of pulmonary artery was demonstrated. Aorta did not appear until pulmonary artery had faded indicating absence of intracardiac shunt (Case 3).

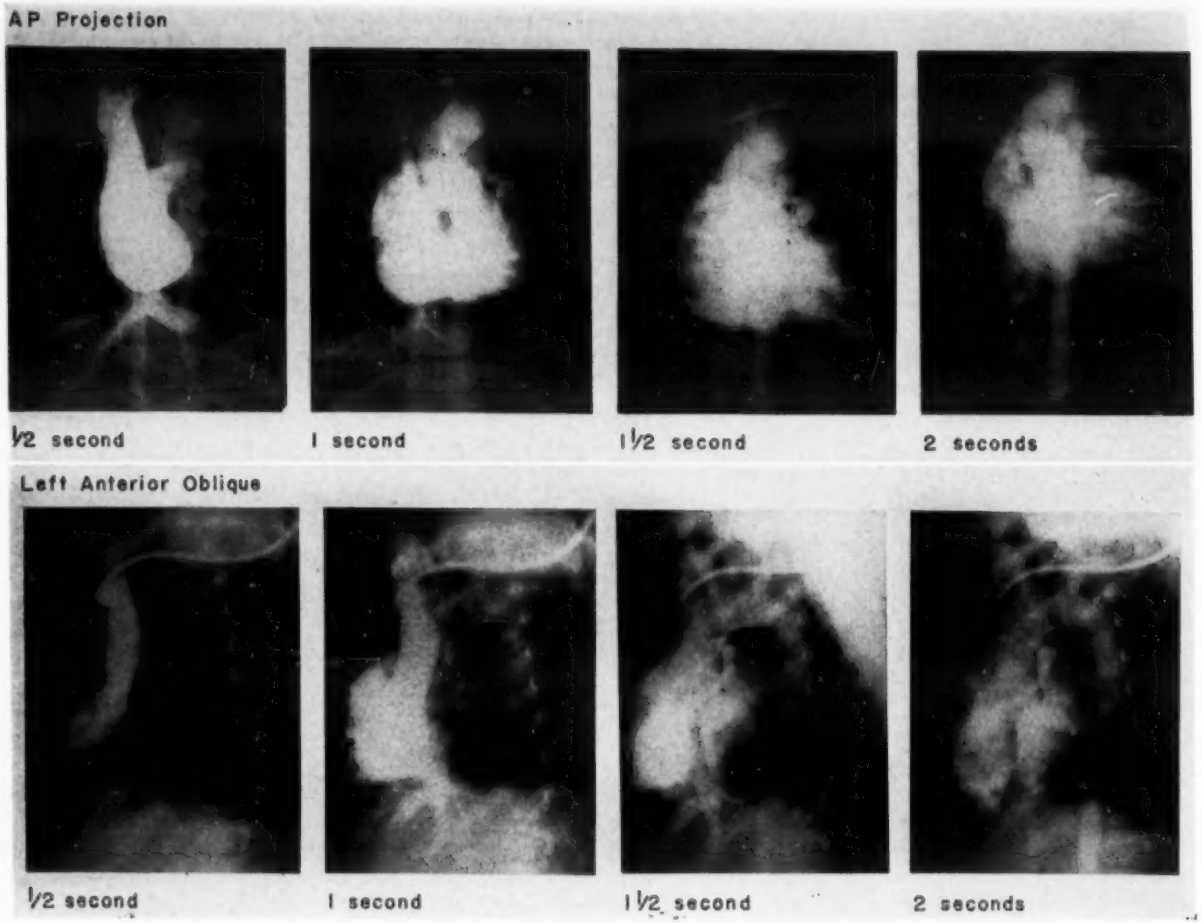


Fig. 5.—Tetralogy of Fallot with atrial septal defect: (pentology). A, AP position. Immediate filling of aorta indicated extreme overriding. Atrial defect was established by catheter. Although insufficient blood supply to lungs was indicated, the pulmonary arteries were identified (A, 1 sec. and B).

B, Left anterior oblique position (Filmed as RPO position). Note extreme dextroposition of aorta. Appearance of pulmonary artery shadow at one second before left ventricle filled excluded transposition (Case 4). Catheter was in superior vena cava.

murmur and thrill were present. $P_2$ equaled $A_2$. Clubbing was marked. No history of squatting. Resting oximetric determinations showed oxygen saturations averaging 75 per cent; after exercise, 63 per cent.

Cardiac catheterization demonstrated pulmonary stenosis with a right ventricular pressure of 105/5 mm. Hg and pulmonary artery pressure of 20/5 mm. Hg. A continuous record obtained during withdrawal of catheter showed abrupt change suggesting valvular stenosis. A catheter was passed through atrial septal defect into both left atrium and left ventricle where oxygen levels varied between 95 and 99 per cent. Oxygen saturation in the femoral artery was 80 per cent. Injection of 0.35 mg./kg. of Evan's blue dye by the method of Swan and Wood[12] failed to indicate an overriding aorta. Angiocardiography (Fig. 6) complemented the above findings by demonstrating the absence of valvular stenosis. Overriding of the aorta was shown by abnormally early aortic filling through an intracardiac shunt. This was followed by normal later filling of the aorta from the left ventricle after the pulmonary arteries had emptied. Blalock-Taussig operation was recommended and performed with excellent immediate results. Resting arterial oxygen saturation levels rose to an average of 88 per cent. Johnson and Johnson[13] have stressed the undesirability of a shunt operation for pulmonary stenosis with a patent foramen ovale because of the danger of increasing left atrial pressure and thus impairing the safety valve function of the atrial defect. To what degree a ventricular septal defect may be compensatory will be observed in this patient.

CASE 6.—B. L., deeply cyanotic female infant 3 months of age, had severe dyspnea and a heart grossly enlarged to the right of the midline. Electrocardiogram showed electrical axis of zero and left ventricular hypertrophy. There were Grade 3 systolic and diastolic murmurs maximal at the third parasternal intercostal space; no thrill. Hemoglobin, 17 Gm. Liver was down 6 cm. and pulsations were equivocal. Ear oximetry determinations averaged 61 per cent saturation.

Angiocardiogram (Fig. 7) demonstrated appearance of dextrocardia as emphasized by Neuhauser[14] in triscuspid atresia with a small atrial septal defect. A representative film showed large right atrium through which dye passed to the left side of the heart without normal pulmonary artery opacification. Abnormal, early aortic filling occurred. Although the aorta originated far to the right, transposition was excluded by evidence of a small unbranched but normally placed pulmonary trunk which appeared promptly and remained opacified after the aorta was no longer visualized (Fig. 7, 4 sec.). In Fig. 7 (3 sec.) can be seen the right pulmonary artery. Functional pulmonary stenosis is shown by the absence of normal pulmonary opacification throughout the entire series. At surgery, hypoplasia of the main pulmonary artery was confirmed. Anastomosis between right pulmonary artery (visualized in Fig. 7, 3 sec.) and the right subclavian artery was accomplished with increase of arterial oxygen saturation levels to 88 per cent.

CASE 7.—S. S., 19-month-old female infant had normal birth and delivery, and there were no illnesses during her first year of life. At 15 months of age cyanosis first occurred with a severe upper respiratory infection which cleared spontaneously. She was first hospitalized at 19 months of age with extreme cyanosis, dyspnea, and anasarca. There was no infection. The infant was underdeveloped, and the heart was grossly enlarged. A precordial bulge was present and the heart-rate was 40 per minute with complete atrioventricular dissociation. A short coarse Grade 4 systolic murmur was present plus a coarse diastolic murmur of equal duration and intensity; no thrill. An enlarged liver pulsated intermittently. An electrocardiogram showed right ventricular hypertrophy with an electrical axis of plus 120 degrees and abnormally high peaked P waves in Lead II. Angiocardiogram favored diagnosis of Ebstein's anomaly (Fig. 8). Extreme right atrial enlargement was shown with its outline persisting throughout the series. Abnormally early aortic filling was demonstrated which indicated a right-to-left atrial shunt or overriding aorta. Absence of a left-to-right atrial shunt was established by finding the oxygen content of right atrial blood the same as in the inferior vena cava. The delay in visualization of the pulmonary vessels is to be expected because of the tricuspid insufficiency inherent in this defect. Normally the lungs empty in a maximum of 2 sec. according to Cooley;[15] in this instance their prolonged opacification is to be expected. Herrmann[16] notes the frequent occurrence of a coarse diastolic murmur in Ebstein's anomaly as observed in this patient. In Lutembacher's syndrome the left-to-right

B, Left anterior oblique position (Filmed as RPO position). Note extreme dextroposition of aorta. Appearance of pulmonary artery shadow at one second before left ventricle filled excluded transposition (Case 4). Catheter was in superior vena cava.

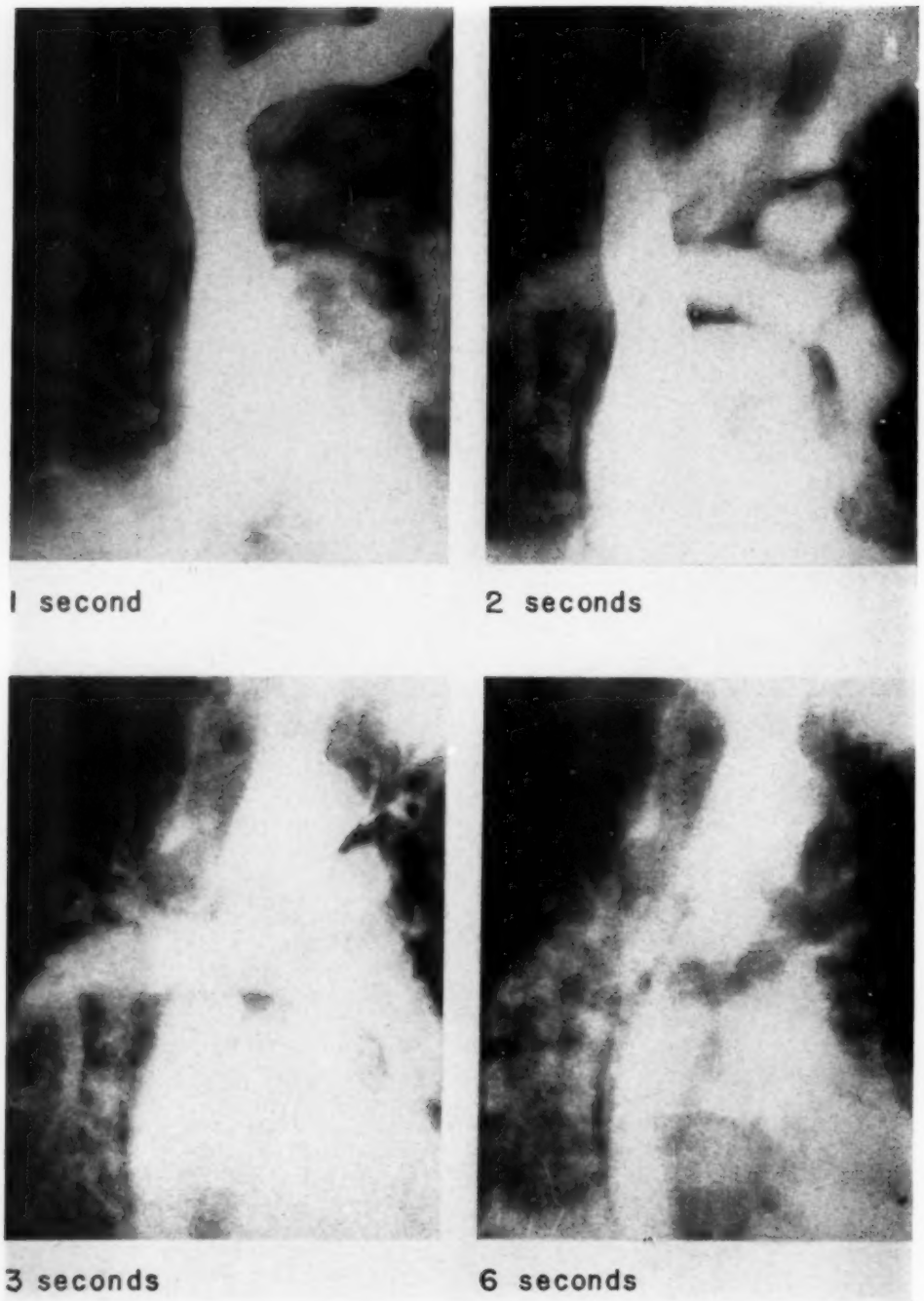


Fig. 6.—Tetralogy of Fallot with atrial septal defect: (pentology). Note abnormally early visualization of aorta. Atrial defect and pulmonic stenosis were established by catheter. Valvular stenosis was thought excluded by absence of a post stenotic dilatation of the pulmonary artery (Case 5).

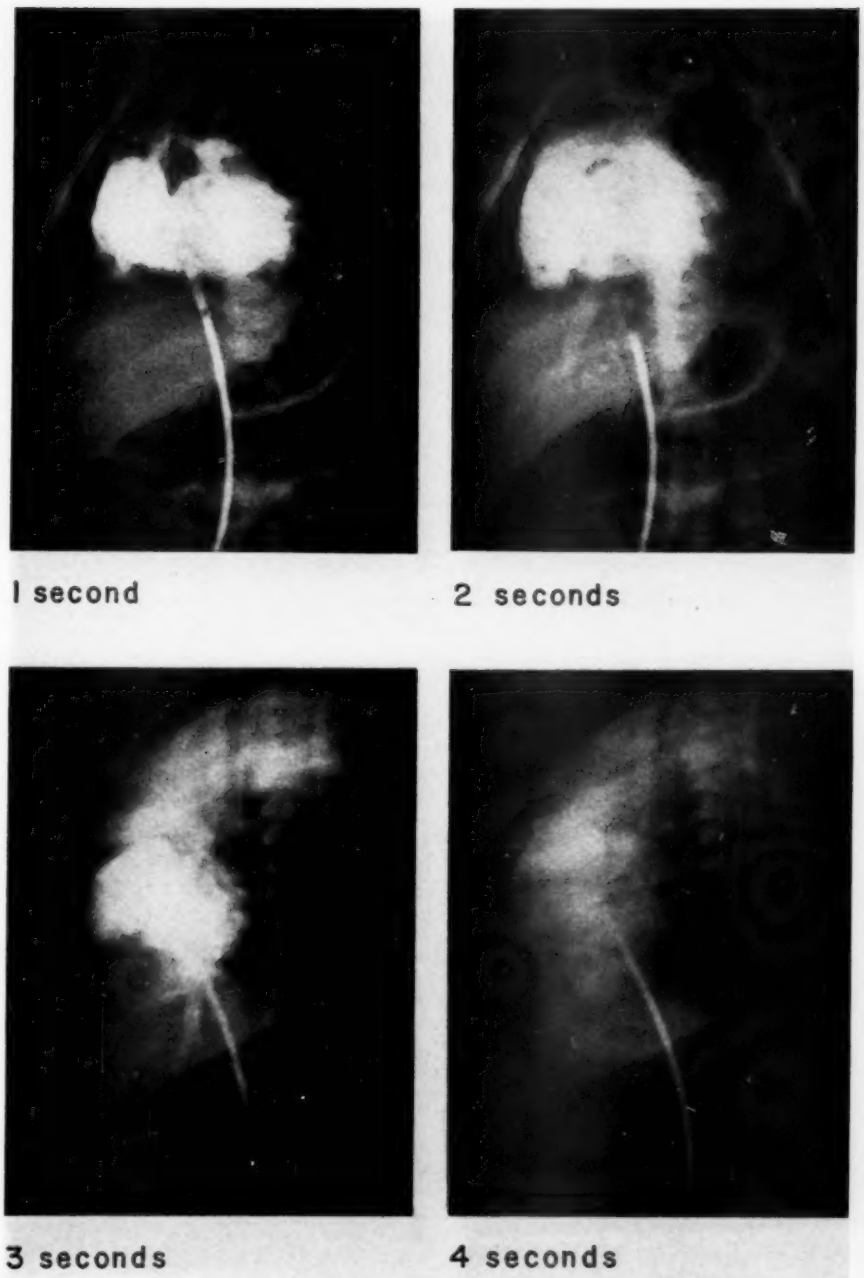


Fig. 7.—Tricuspid atresia with pulmonic stenosis. AP projection (1 and 2 sec.) demonstrated early filling of aorta without opacification of the lungs. Left anterior oblique films showed existence of small right pulmonary artery (3 sec.) and normally situated root of main pulmonary artery (4 sec.).

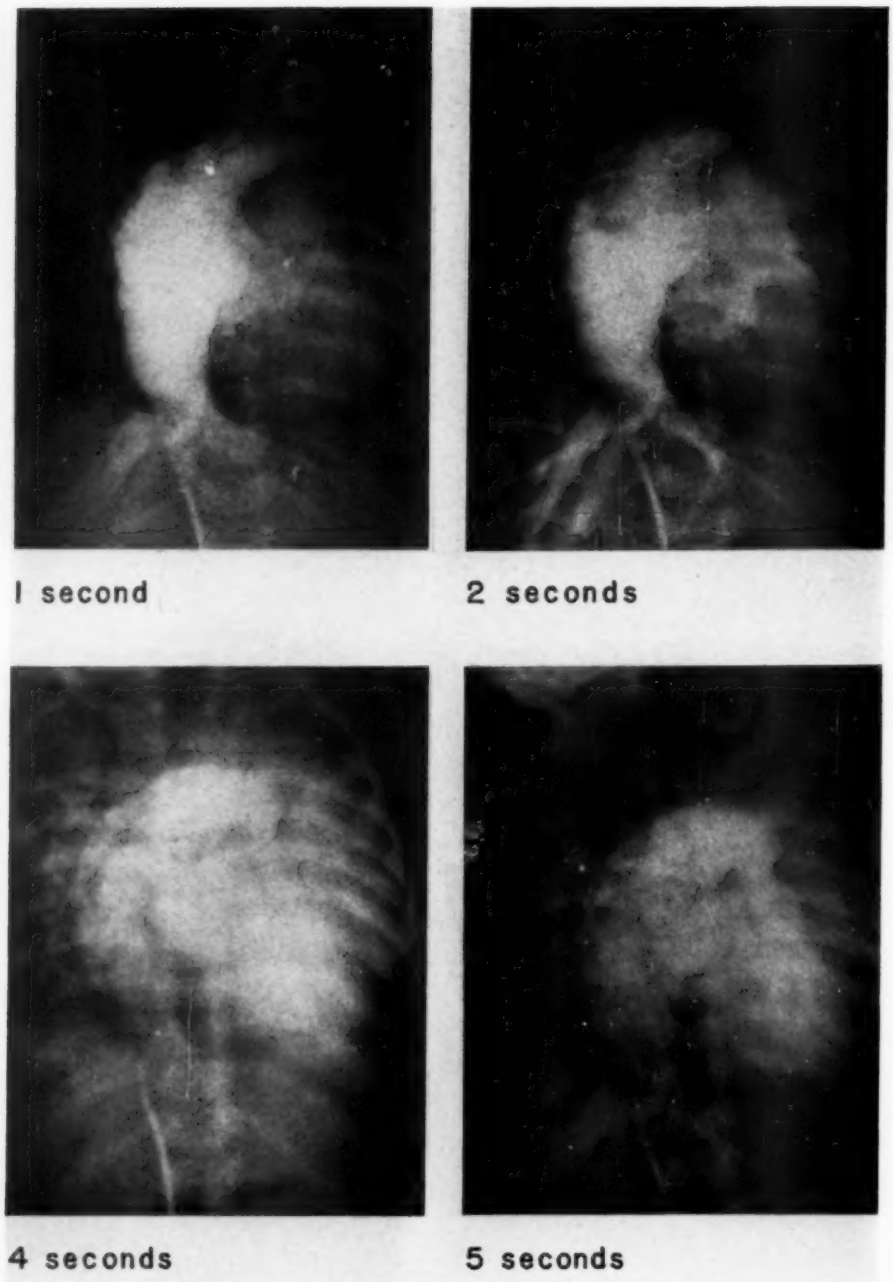


Fig. 8.—Ebstein's anomaly: Large right atrium was distended throughout series. Abnormally early aortic filling was through a right-to-left atrial shunt which was established by catheter. Child had complete atrioventricular dissociation, right ventricular hypertrophy and a short, coarse diastolic murmur.

atrial shunt prevents early aortic filling as noted here. Other described congenital defects are not consistent with the combined clinical, electrocardiographic, and angiocardiographic findings present in this case.

## COMMENT

A number of earlier electrocardiographic control observations by the author during injection of the dye showed sharp T-wave inversions over the left ventricle which lasted for five to sixty seconds. Associated runs of ventricular tachycardia as noted by Zinn and associates[17] were not observed.

On the premise of preventing an increase in coronary anoxia by this method of juxta-cardiac injection as cautioned by Dr. George R. Herrmann, consulting cardiologist, it was felt that replacing the dissolved blood nitrogen with oxygen might be beneficial, especially in cyanotic patients. Therefore, in all cases oxygen by mask has been given for five minutes prior to, during, and after injections of the dye. Marked lessening of T-wave inversions has occurred. In addition, the routine employment of oxygen inhalations has assured the physical nearness of apparatus to insert and employ an airway in case of emergency, although it has never been necessary. Thus far, the only reaction to the dye has been the transitory appearance of widespread neuromuscular fasciculations. Vital signs were unaffected. No pain has occurred with the injections and the patients' discomfort has been negligible. This has been due in part to the cautious use of supplemental intravenous Demerol before each injection to the point of inducing light narcosis. Also important has been the employment of 70 per cent sodium acetrizoate* which contains a significantly higher concentration of mollecular iodine and is better tolerated by the patients in our experience. No difficulty has resulted from repeated injections as required.

Juxta-cardiac injection of the dye through a large tube goes far toward assuring diagnostic films. The bolus effect of the dye entering the heart in relatively undiluted form with less caval reflux means that the period during which a single chamber is opacified is considerably reduced. As a result the diagnostic reliability of continued opacification and reopacification of individual chambers is enhanced. Fig. 9 shows continued opacity of a large right atrium after filling of the left ventricle and aorta in a case of atrial septal defect. Admittedly, anomalous pulmonary venous drainage remains a possibility.

The determination of circulation time before injection of the dye has not been helpful. In all cases, satisfactory visualization of the left ventricle and aorta has occurred in an average of 5 seconds and a maximum of 6 seconds from the start of injection. Thus at least two seconds may be subtracted from the filling time of various chambers as given by experienced observers.[18,19] Presumably this shortening of time results from exclusion of the variable factors of dilution, venous patency, collateral venous filling, and peripheral venous pressure. The only predictable delay in aortic filling (approximately one-half to one second) has occurred with the right atrium in a position of dependency as in the left anterior oblique position (actually RPO) as compared with the right anterior oblique position (LPO).

*Urokon Sodium.

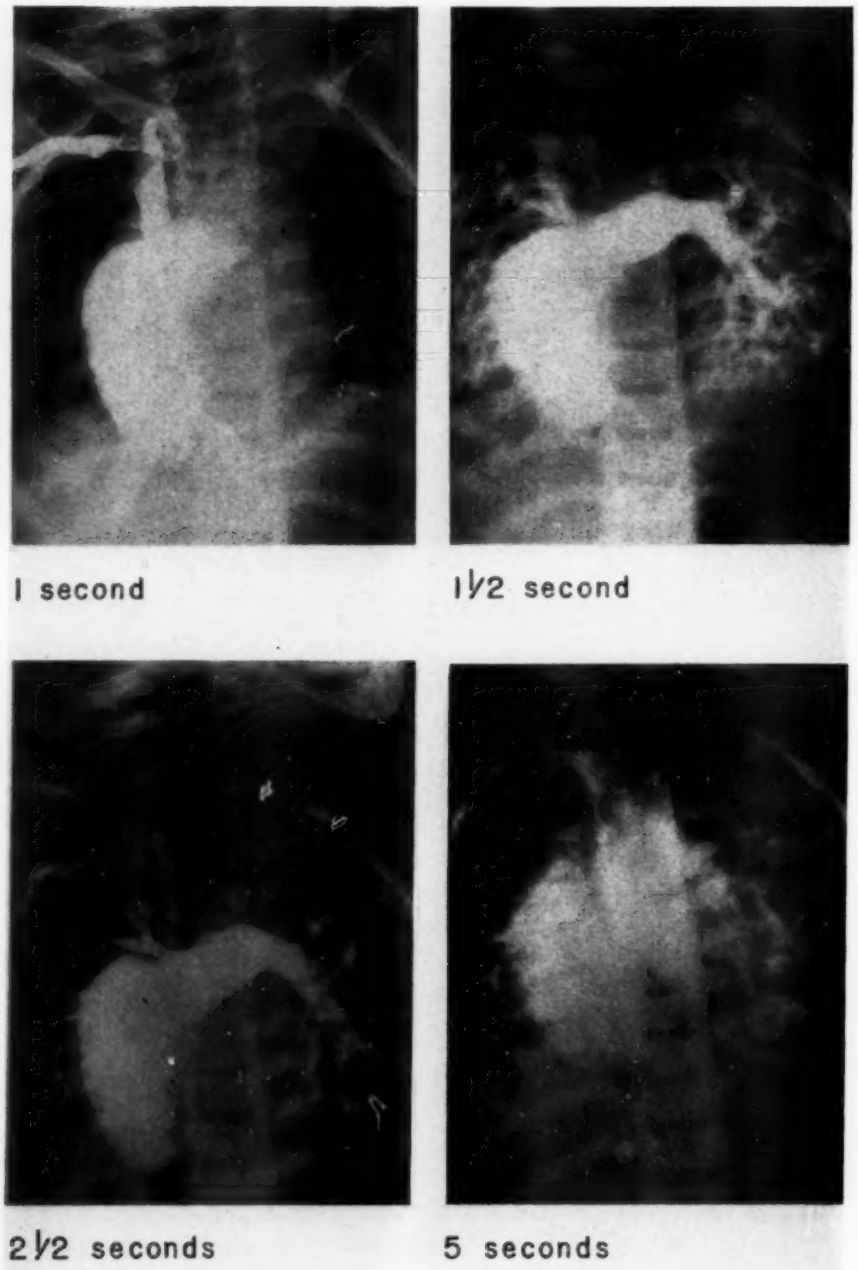


Fig. 9.—Atrial septal defect. Continued opacification of the right atrium and lungs was seen long after injection had been completed at 1 sec. At 5 sec. the left ventricle and aorta appeared while the left atrium in the midline continued to shunt blood to the right side of the heart. Anomalous pulmonary venous drainage into the right atrium was considered.

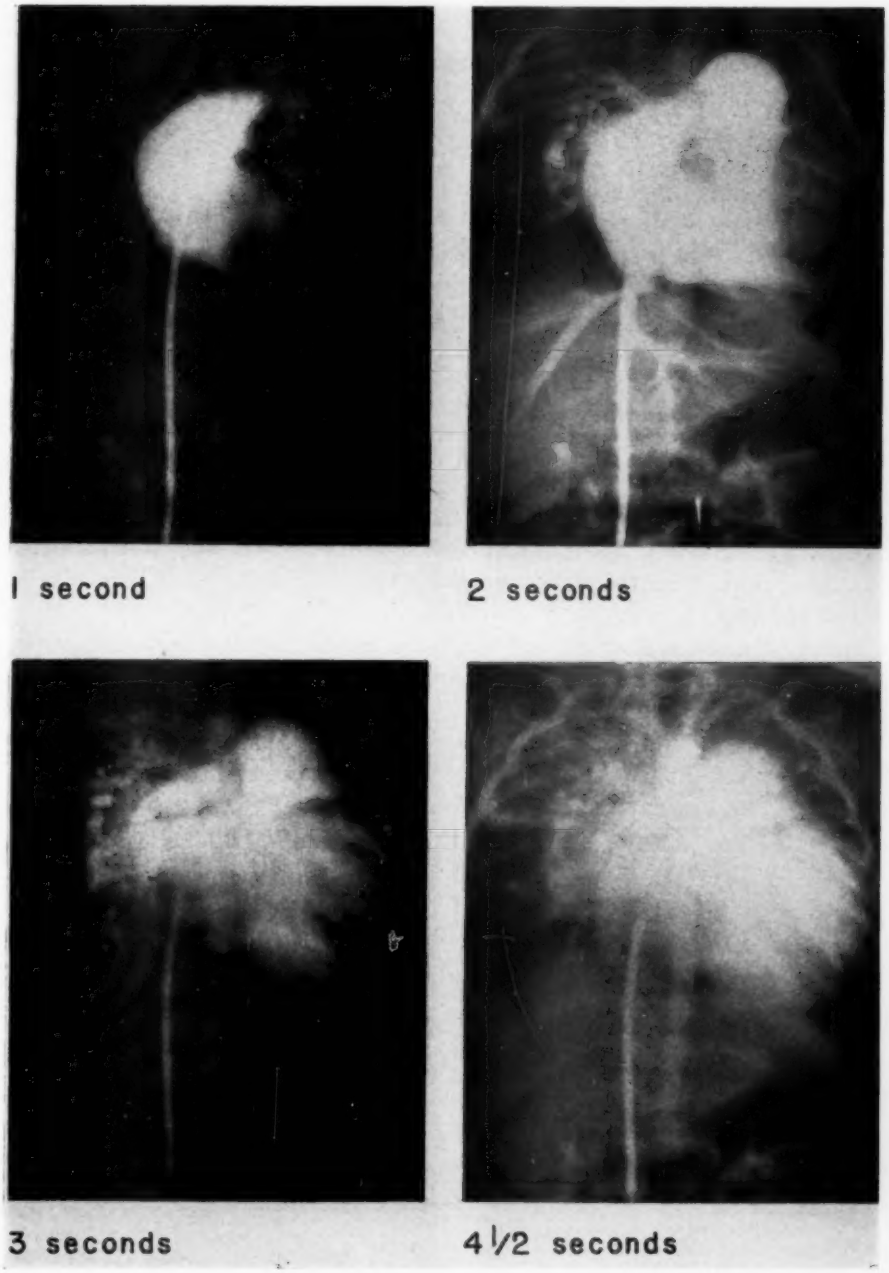


Fig. 10.—Eisenmenger's syndrome: Aorta filled at 2 sec. which indicated dextroposition and high ventricular septal defect (overriding). Pulmonary artery was dilated and lungs filled normally. Large right ventricle was outlined at 2 sec. Intact atrial septum was indicated by emptying of the right atrium (surrounding tip of catheter) before 3 sec. Normal left atrium was visualized extending to patient's right, across the midline and above the empty right atrium.

In a number of instances it has not been necessary or of likely help to continue with catheterization after angiocardiograms have been filmed. Thus, Fig. 10 demonstrates premature aortic filling (high ventricular septal defect) with a prominent pulmonary artery segment. The absence of an atrial septal defect is shown by satisfactory emptying of the right atrium from two seconds on. The dye extending across the midline overlying the tip of the catheter is in the superimposed left atrium. Clinically, the infant had severe cardiac failure with pulmonary edema as a prominent feature. Cyanosis was minimal. An electrocardiogram showed right ventricular hypertrophy. Grade 4 systolic murmur was loudest over the fourth parasternal intercostal space, and a thrill was present. It was felt that criteria for diagnosis of Eisenmenger's complex had been demonstrated despite its reputed rarity as recorded by Bing and associates,[20] and that catheterization was unnecessary.

## SUMMARY

The routine employment of both angiocardiography and cardiac catheterization as a combined procedure has been described. The degree to which their respective findings complement and amplify one another has been illustrated by several cases.

Certain procedural modifications have been described which significantly reduce the total time and personnel required for the performance of these studies without making them more hazardous. Particular emphasis has been placed on use of the basilic vein high in the arm for the insertion of a polyethylene catheter. Through it a less than usual amount of dye has been injected close to the heart. This has resulted in dependable visualization of the left heart and aorta by angiocardiography. Subsequently, the same vein has been used for catheterization, as a part of the same procedure.

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# ARTIFICIAL REDUCTION OF THE HEART EFFORT

## The Effect of The Association of Hexamethonium Bromide and Sodium Amytal

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### INTRODUCTION

THE dynamic effort of the heart as a pump can be measured according to the physical laws governing work and power. A formula which is considered as a classical expression[1-3] of the hemodynamics of the heart is the following:

$$\text{Cardiac Work} = \text{Output} \times \text{mean arterial pressure} + \frac{\text{mass} \times \text{speed}^2}{2\,G}$$

The second part of this equation, dealing with mass, speed, and gravitation, concerns kinetic energy and is neglected by most authors[4-9] for two reasons. The first is the small percentage of this additional contribution to the product output × mean pressure; the second consists in the difficulty of measuring two factors, mass and speed in every case. This voluntary simplification of the complete formula, however, may introduce a certain degree of error in cases where the speed of circulation is high, as in aortic stenosis for instance, or where the output is increased as in thyrotoxicosis. Variations range from 2 to 5 per cent for the left ventricle and may even reach 25 per cent for the right.[10-12] Since our research is largely concentrated on the work of the left ventricle, the margin of error is easily accepted with regard to the approximation already contained in the calculation of the output (10 to 15 per cent) and in the determination of the mean arterial pressure from the humeral artery rather than from the aorta.[13,14]

The object of the study reported in this paper was to test the possibility of lowering the heart's work below its normal level, i.e., below the basal condition at rest, by means of therapeutic agents. The study was inspired by the possible usefulness of economy in the work of the heart induced by a lesser need of the periphery.

Two chemical compounds were used for this purpose: (1) Hexamethonium bromide, whose prominent hypotensive effect is well known,[15,16] and which sometimes has also a small depressing action on cardiac output;[17,18] and(2) Sodium Amytal, which besides having a hypnotic effect displays a hypotensive action and lessens the metabolic exchanges of the body.[19,20]

Received for publication Sept. 14, 1953.

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These two medicaments were chosen because neither of them could have a paralyzing effect on the heart itself when given in therapeutic dosages. Hexamethonium lowers the peripheral resistance; this in turn reduces the pressure necessary to circulate the blood. The lessening of the metabolic rate by Sodium Amytal diminishes the circulatory need, i.e., the cardiac output.[19]

In the course of this study, use is made of the simplified formula for cardiac work:

Cardiac work (kilogram/meter) = Cardiac output (liter/min.) × mean arterial pressure (mm. Hg) × 0.0133.

The mean arterial blood pressure is determined for the whole cardiac cycle and for the systolic period.[21,22]

The dynamic action of the heart takes place during systole only. In order to calculate the work of the heart itself, the output must be multiplied by the mean systolic arterial pressure. The product output × mean cycle pressure measures the so-called "peripheral work"[22] and corresponds to the amount of energy required to overcome peripheral resistance and maintain a continuous flow.

Wiggers' diagram[21] clearly demonstrates the mean pressures employed in the calculation of the two kinds of work. Wiggers also compares two areas called X and Y which represent the static and dynamic effort of the heart.[21,23,24]

Another entity, named the "heart power", may be calculated from the dynamic work, by dividing the latter by the time during which it is performed, i.e., the systolic time. It must be emphasized that the concept of power does not correspond to the maximal contractile force of the heart but represents the actual degree of mechanical activity.

## METHODS

The two essential terms of the simplified formula for heart work are cardiac output and mean arterial blood pressure. The cardiac output was measured by Stewart-Hamilton's dye-dilution method[25-27] with Evans blue, which is considered as accurate as Fick's method.[28-30] The values for mean systolic and mean cycle arterial pressures were calculated by planimetric integration of sphygmographic recordings from the humeral artery using Warbφrg-Hansen's manometer[31] and a Cournand indwelling needle.[32]

The experimental study was made on thirteen patients: seven hypertensive patients without heart failure, and six with neither hypertension nor heart disease (Table I). They were kept fasting for twelve hours. During the test, they rested in their beds in a semielevated position. Approximately twenty minutes after the needles were inserted in the left humeral artery and in the right basilic vein, the different recordings and samplings were started for the basal metabolic rate, the cardiac output, and the arterial sphygmogram. As soon as these preliminary steps had been taken, Sodium Amytal was administered orally (0.20 to 0.40 Gm. according to the individuals). Forty-five to sixty minutes later, after an initial

TABLE I.

| NO., PATIENT, AGE, SEX DIAGNOSIS | AMYTAL (GM.) VEGOLYSEN (MG.) (HMB) | (%) B.M. RATE | | | CARDIAC OUTPUT LITER/MIN. | | | INTRA-ARTERIAL BLOOD PRESSURE (MM. HG) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | MEAN CYCLE PRESSURE | | | | | MEAN SYSTOLIC PRESSURE | | |
| | | | | | | | | MAXIMUM AND MINIMUM | | MEAN | | VAR. (%) | MEAN | | VAR. (%) |
| | | BEFORE | AFTER | VAR. (%) | BEFORE | AFTER | VAR. (%) | BEFORE | AFTER | BEFORE | AFTER | | BEFORE | AFTER | |
| 1 PI 54 M. Gastritis | A 0.40 V 10 | +19 | +4 | −12.5 | 5.170 | 4.960 | − 4 | 168/106 | 125/85 | 134 | 107 | −20 | 149 | 117 | −21 |
| 2 MA 34 M. Hypertension Nephritis | A 0.40 V 100 | +25 | +16 | −7 | 5.200 | 5.000 | − 4 | 220/166 | 167/127 | 193 | 146 | −24 | 212 | 160 | −24 |
| 3 DU 56 M. Arteriosclerosis of the legs | A 0.40 V 20 | +42 | +20 | −15 | 5.180 | 4.620 | −10 | 169/119 | 131/96 | 140 | 105 | −25 | 162 | 115 | −27.5 |
| 4 MO 50 M. Hypertension Auricular fibrill. | A 0.40 V 10 | +44 | +39 | − 3.5 | 2.580 | 2.230 | −13 | 200/176 | 145/105 | 182 | 122 | −33 | 200 | 135 | −32.5 |
| 5 JA 65 M. Arteriosclerosis of the legs | A 0.20 V 15 | 0 | +15 | +15 | 3.100 | 3.650 | +17 | 145/80 | 94/61 | 97 | 76 | −21 | 117 | 86 | −26 |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | CO 51 M. Chron. bronchitis | A 0.30 V 30 | +38 | +11 | −19 | 6.170 | 5.300 | −14 | 140/96 | 117/85 | 112 | 98 | −12 | 128 | 115 | −10 |
| 7 | BR 69 F. Hypertension (Essential) | A 0.30 V 20 | +18 | +16 | −11 | 4.080 | 3.900 | − 4 | 153/87 | 141/92 | 114 | 115 | + 1 | 134 | 131 | − 2 |
| 8 | SA 69 F. Hypertension (Essential) | A 0.20 V 7.5 | + 8 | 0 | − 7.5 | 4.280 | 2.950 | −31 | 185/140 | 145/96 | 161 | 112 | −30 | 170 | 132 | −22 |
| 9 | AR 67 F. Hypertension (Essential) | A 0.30 V 10 | — | — | — | 3.000 | 2.000 | −33 | 190/112 | 128/71 | 144 | 86 | −40 | 169 | 110 | −35 |
| 10 | AE 70 M. Arteriosclerosis (Senile) | A 0.30 V 45 | — | — | — | 4.420 | 3.960 | −10 | 159/90 | 153/100 | 121 | 127 | + 5 | 145 | 140 | − 3.5 |
| 11 | SO 43 F. Hypertension (Essential) | A 0.20 V 10 | — | — | — | 4.850 | 2.910 | −40 | 220/150 | 129/80 | 180 | 98 | −45 | 202 | 120 | −41 |
| 12 | RO 58 F. Cirrhosis of the liver (Alcoholic) | A 0.30 V 40 | — | — | — | 4.640 | 3.900 | −16 | 172/123 | 167/124 | 147 | 142 | − 3.5 | 168 | 158 | − 6 |
| 13 | KO 68 F. Hypertension (Obesity) | A 0.30 V 7 | — | — | — | 3.800 | 2.850 | −25 | 193/136 | 148/101 | 162 | 120 | −26 | 182 | 134 | −26 |

TABLE II

| PATIENT | PERIPHERAL RESISTANCE DYNES SEC. CM.$^{-5}$ | | VARIAT. (%) | PERIPHERAL WORK (CARDIAC CYCLE) KILOGRAMMETER/MIN. | | VARIAT. (%) | WORK OF THE HEART (SYSTOLIC) KILOGRAMMETER/MIN. | | VARIAT. (%) | SYSTOLIC DURATION SEC./100 | | RATE/MIN. | | SYSTOLIC DURATION OVER 1 MIN. (SEC.) | | POWER CV/1000 | | VARIAT. (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | BEFORE | AFTER | | BEFORE | AFTER | | BEFORE | AFTER | | BEFORE | AFTER | BEFORE | AFTER | BEFORE | AFTER | BEFORE | AFTER | |
| 1 PI | 2060 | 1720 | −16.5 | 9.14 | 7.05 | −23 | 10.13 | 7.71 | −24 | 32 | 30 | 62 | 64 | 19.8 | 19.2 | 6.8 | 5.3 | −22 |
| 2 MA | 2960 | 2330 | −21 | 13.3 | 9.7 | −27 | 14.6 | 10.6 | −27 | 27 | 25 | 75 | 88 | 20.2 | 22.0 | 9.6 | 6.4 | −33 |
| 3 DU | 2150 | 1810 | −15.5 | 9.6 | 6.4 | −33 | 11.1 | 7.0 | −36 | 32 | 28 | 75 | 87 | 24.0 | 24.3 | 6.1 | 3.7 | −39 |
| 4 MO | 5740 | 4360 | −22 | 6.2 | 3.6 | −42 | 6.8 | 4.0 | −41 | 17 | 18 | 88 | 60 | 14.9 | 10.8 | 6.1 | 4.9 | −19 |
| 5 JA | 2500 | 1660 | −33 | 4.0 | 3.6 | −10 | 4.8 | 4.1 | −13 | 34 | 33 | 66 | 60 | 22.4 | 19.8 | 2.8 | 2.7 | − 3 |
| 6 CO | 1440 | 1470 | + 2 | 9.1 | 6.9 | −24 | 10.5 | 8.1 | −23 | 29 | 26 | 86 | 94 | 24.9 | 24.4 | 5.6 | 4.4 | −21 |
| 7 BR | 2200 | 2350 | + 7.5 | 6.1 | 5.9 | − 3 | 7.2 | 6.7 | − 7 | 28 | 30 | 75 | 79 | 21.0 | 23.7 | 4.5 | 3.7 | −17 |
| 8 SA | 3000 | 3020 | + 0.6 | 9.1 | 4.3 | −52 | 9.6 | 5.1 | −47 | 34 | 31 | 64 | 64 | 21.7 | 19.8 | 5.9 | 3.4 | −42 |
| 9 AR | 3830 | 3430 | −10 | 5.7 | 2.3 | −59 | 6.7 | 2.9 | −56 | 32 | 32 | 71 | 71 | 22.7 | 22.7 | 3.9 | 1.7 | −56 |
| 10 AE | 2180 | 2560 | +17 | 7.1 | 6.6 | − 7 | 8.6 | 7.3 | −16 | 34 | 30 | 58 | 80 | 19.7 | 24.0 | 5.7 | 4.0 | −30 |
| 11 SO | 2960 | 2690 | − 9 | 11.6 | 3.7 | −68 | 13.0 | 4.6 | −64 | 28 | 24 | 86 | 83 | 24.0 | 19.9 | 7.2 | 3.0 | −58 |
| 12 RO | 2520 | 2900 | +14 | 9.0 | 7.3 | −19 | 10.3 | 8.1 | −21 | 24 | 22 | 100 | 100 | 24.0 | 22.0 | 5.7 | 4.8 | −15 |
| 13 KO | 3400 | 3360 | − 1 | 8.1 | 4.5 | −44 | 9.1 | 5.0 | −45 | 24 | 23 | 96 | 100 | 23.0 | 23.0 | 5.3 | 2.9 | −45 |

drop of pressure, an intravenous injection of 1 per cent hexamethonium bromide was gradually performed until a second drop of pressure was observed (7.5 to 100 mg. depending on the case). About fifteen minutes later, when the pressure was stabilized, a second set of recordings and samplings for output determination, intra-arterial sphygmogram, and metabolic rate was started.

Sodium Amytal usually provoked a stage of somnolence, the patients remaining, however, sufficiently awake for the second measurement of metabolic rate. The injection of hexamethonium was stopped when the systolic pressure had fallen to approximately 110 mm. Hg. In two instances a state of slight collapse was noticed which was overcome by lowering the patient into a supine position.

Hamilton's method provides a measure of the "circulation time" which is the time elapsing between the injection of Evans blue into an arm vein and the appearance of the dye in the artery of the other arm. The calculation of the cardiopulmonary blood volume is based on the following formula: Volume = Output × mean time. The mean time of passage of the dye is obtained by ascertaining the center of gravity of the dilution curve.[25,33]

The intra-arterial pressure curve is used for measuring the systolic duration, the pulse rate, and Wiggers' areas X and Y. Following this author we noted also the intra-arterial "equilbrium pressure"[21] of the arm, which is the static pressure persisting inside the artery after total interruption of the circulation by an arm cuff placed above the Cournand needle. This pressure is supposed to be related to the vascular tonus.

Hematocrit values at the time of the first and second recordings are also included in the table of results.

## RESULTS

All the results are set out in detail in the three tables.

As a consequence of the combined action of hexamethonium bromide and Sodium Amytal, the systolic work of the heart, as well as the peripheral work, was reduced in all cases (Table II). The average reduction was 32 per cent for the systolic work (7 to 64 per cent), and 31.5 per cent for the peripheral work (3 to 68 per cent).

The basal metabolic rate was lowered from 3.5 to 19 per cent in seven cases. In one case it was increased by 15 per cent (Table I).

A diminution of the cardiac output was achieved in twelve out of the thirteen cases, the values ranging from 4 to 40 per cent, (mean 17 per cent); the output was increased by 17 per cent in one case, the one in which the metabolic rate rose during the test (Table I).

The mean arterial blood pressure was lowered in eleven out of the thirteen cases for the cycle pressure (from 3.5 to 40 per cent, mean 24 per cent), and in all cases for the systolic pressure (from 2 to 40 per cent, mean 21 per cent) (Table I).

The peripheral resistance was diminished in eight cases (from 1 to 33 per cent; mean 16 per cent); it was increased in the five others (from 0.6 to 17 per cent; mean 8.2 per cent) (Table II).

TABLE III

| PATIENT | | CIRCULATION TIME SEC. | | MEAN TIME SEC. | | HEART-LUNG VOLUME LITER | | EQUILIBRIUM PRESSURE MM./HG | | AREA X $MM^2./10$ | | AREA Y $MM^2./10$ | | QUOTIENT X/Y | | HEMATOCRIT (%) GL. R. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | BEFORE | AFTER | BEFORE | AFTER | BEFORE | AFTER | BEFORE | AFTER | BEFORE | AFTER | BEFORE | AFTER | BEFORE | AFTER | BEFORE | AFTER |
| 1 | PI | 10.5 | 13 | 20 | 23 | 1.720 | 1.900 | 48 | 40 | 21.2 | 10.2 | 50.4 | 26.5 | 0.399 | 0.390 | 38.5 | 37.5 |
| 2 | MA | 18 | 22 | 27 | 33 | 2.340 | 2.750 | 58 | 53 | 9.0 | 6.8 | 36.8 | 30.6 | 0.244 | 0.220 | 48 | 46 |
| 3 | DU | 19.5 | 16 | 31.5 | 26 | 2.710 | 2.000 | 44 | 38 | 13.4 | 7.6 | 35.6 | 38.6 | 0.376 | 0.194 | 45 | 44 |
| 4 | MO | 24 | 28 | 62 | 53 | 2.660 | 1.970 | — | — | 2.57 | 6.5 | 23.1 | 22.7 | 0.108 | 0.289 | 57 | — |
| 5 | JA | 15 | 26 | 35 | 43 | 1.800 | 2.600 | 33 | 15 | 19.6 | 19.8 | 42.8 | 46.8 | 0.458 | 0.429 | 40 | 39 |
| 6 | CO | 14 | 13.5 | 23 | 23 | 2.360 | 2.000 | 26 | 41 | 13.9 | 7.4 | 41.4 | 21.3 | 0.330 | 0.347 | 47 | 46 |
| 7 | BR | 21 | 16 | 22 | 62.5 | 1.500 | 1.880 | 43 | 48 | 13.2 | 14.4 | 26.7 | 34.2 | 0.480 | 0.420 | 40 | 38.5 |
| 8 | SA | 16 | 20.5 | 28.5 | 36 | 2.030 | 1.770 | 67 | 39 | 10.6 | 17.6 | 50.4 | 47.6 | 0.200 | 0.375 | 43 | 41 |
| 9 | AR | 16 | 18 | 26 | 31 | 1.300 | 1.030 | — | — | 18.8 | 5.2 | 36.8 | 24.9 | 0.510 | 0.213 | 34 | 32 |
| 10 | AE | 30 | 20 | 48 | 33 | 3.500 | 2.170 | 40 | 35 | 21.1 | 13.2 | 34.8 | 42.9 | 0.670 | 0.300 | 44 | 43 |
| 11 | SO | 8 | 14 | 15 | 25 | 1.210 | 1.220 | 49 | 26 | 14.9 | 17.0 | 43 | 34.5 | 0.346 | 0.490 | 47 | 46 |
| 12 | RO | 10 | 16 | 18.5 | 27 | 1.430 | 1.750 | 36 | 31 | 14.2 | 8.7 | 34.4 | 32.1 | 0.410 | 0.260 | 38 | 36 |
| 13 | KO | 19 | 22 | 33 | 37.5 | 2.090 | 1.780 | — | — | 11.8 | 7.3 | 35.6 | 23.4 | 0.330 | 0.310 | 59 | 58 |

The relationships among the three data, output, pressure and resistance, were twofold: when the mean blood pressure was lowered to such an extent as to exceed proportionally the reduction of the output, the peripheral resistance was diminished (cases 1 to 5, 9, 11, 13). On the other hand, when the peripheral resistance was observed to increase, the output fell proportionally more than the mean blood pressure (cases 6 to 8, 10, 12).

The total systolic time per minute of heart activity was increased in four cases, reduced in seven, and remained unchanged in two.

The heart power was diminished by 30 per cent. This reduction was not necessarily of the same value as the reduction of the work itself, since the concept of power depends on the systolic duration per minute. The latter was seen either to increase or to diminish during the test, according to the individual. Power was less reduced than work in seven cases (1, 4, 5, 6, 8, 11, 12), more reduced in four cases (2, 3, 7, 10), and unchanged in two cases (9, 13) (Table II).

Variations were observed in the cardiopulmonary blood volume which did not seem to follow any rule; in six cases this value was increased, in seven it was reduced. The same was true of circulation time which rose in nine cases and fell in four (Table III).

Hematocrit values were constantly lowered suggesting a change of the ratio of plasma to cells as a consequence of the drop in blood pressure. The "equilibrium pressure" and the variations of the quotient X/Y did not add useful information to our conclusions.

## DISCUSSION

From the results obtained it appears that the object of this study, the attempt to reduce the cardiac work by hexamethonium bromide plus Sodium Amytal, has been successfully achieved. Whether this reduction of about 30 per cent really represents an economy in the cardiac reserve is open to discussion.

During this test the cardiac output may be reduced by two distinct processes: one is the lowering of the basal metabolic rate by Sodium Amytal; the other is conditioned by the diminished venous return to the heart as a result of dilatation of the vascular bed by hexamethonium bromide. The latter procedure has in fact already been shown to lighten the burden on a deficient heart in the case of congestive failure.

The largest contribution to the lowering of the blood pressure is certainly brought about by hexamethonium bromide. Sodium Amytal, given about three quarters of an hour before hexamethonium, was also followed by a fall in blood pressure in one-half of the cases.

Cases 9 and 11 showed at the same time, a large reduction in cardiac output (respectively, 33 and 40 per cent; and blood pressure, 35 and 41 per cent). Clinically these two patients displayed symptoms of slight vascular collapse, which was readily overcome by placing them in a supine position. The figures which represent the variations in the amount of work (−56 and −64 per cent) and in the degree of power (−56 and −58 per cent) are striking and correspond to a state of deep rest of the heart. In these two cases the heart was spared not only by

the reduction of the peripheral needs but also in part by a decrease in the venous return. At a more advanced stage, the vascular collapse would produce a critical situation on account of the scanty venous return to the heart, which might no longer be able to meet the peripheral demand.

In the course of these experiments, two mechanisms contribute to the reduction of cardiac work. The first consists in the lightening of the peripheral demand, the second in the reduction of the venous return which induces a decreased output. This second mechanism is beneficial as long as it occurs in a moderate degree; otherwise a state of collapse may ensue, which does more harm than good.

It seems that each time the output is only slightly lowered, this is not so much due to an exaggerated venous dilatation as to a lowered metabolism; the drop in pressure is, then, a direct consequence of the reduction of the peripheral resistance. When the output is greatly diminished, a large reduction in the venous return may be suspected with a steady or increased resistance. In such cases the pressure drops more as a result of the diminished stroke volume than by the reduction of the arterial tonus.

The two types of work, that of the heart itself and the peripheral work, underwent a parallel reduction (31.5 and 32 per cent). This confirms their interdependence. When one varies, the other is modified in the same proportion. The slight differences to be noted in our figures are within the margin of error. We tried to obtain a reduction of the systolic work by reducing the needs of the periphery and have been successful in most cases.

It is readily accepted that by combating hypertension the load on the left ventricle is lightened. Kelley[34] recently applied this idea to the treatment of cardiac failure not hypertensive in origin by the successful use of hexamethonium bromide. Our cases, which were not selected and exclude this category, suggest that the economical effect of hexamethonium bromide combined with Sodium Amytal may become a therapeutic effect in case of failure. In contrast to digitalization, which strengthens the myocardium in order to restore an active circulation, this procedure aims at lowering the body requirements and induces the periphery to adapt itself to the weakened heart. This resembles, to a certain extent, the use of morphine as a cardiac sedative which is sometimes considered as effective as digitalis in heart failure. For similar reasons thyroidectomy has been proposed in heart failure even in the absence of hyperthyroidism. In the field of surgery artificial hibernation[35] may be also classed as an attempt of the same kind.

We observed in addition that the heart power was reduced by 30 per cent on the average. The cases may be divided into two groups in this respect. In the first, the power was diminished less than the work (7 of 13 patients), in the second, the opposite occurred (4 of 13 cases). There was no change in two cases. The effect noted in the second group appears more rational and economical from the point of view of the heart strain.

## SUMMARY AND CONCLUSIONS

The object of this study was to reduce the cardiac work below its level at rest. This was effected with the help of two medicaments, hexamethonium bromide and Sodium Amytal, whose action on blood pressure and metabolic rate are well known.

The cardiac work, which is performed during the systolic part of the cycle only, is expressed according to the simplified formula: Work = Output × Mean Systolic Pressure. The systolic time itself being a variable, the intensity of the heart effort developed for a given amout of work is subject to variations. This consideration introduces the concept of the mechanical power of the heart.

Thirteen cases submitted to hemodynamic measurements before and after the administration of hexamethonium bromide and Sodium Amytal, seven hypertensive patients and six without hypertension.

The heart work was observed to decrease by 30 per cent on the average. The economy realized in this manner resulted partly from the diminished peripheral requirements (resistance and metabolism) and partly from a decreased venous return to the heart.

The heart power was similarly reduced by 30 per cent on the average, but according to variations in the systolic time this reduction was greater or smaller than the work's reduction itself. When the heart power is more diminished than the heart work, the cardiac economy is considered still greater.

Both the peripheral resistance and the metabolic rate definitely respond to hexamethonium bromide and Sodium Amytal even when given in small doses. With larger doses the effects can go beyond an economical and harmonius reduction and even lead to circulatory collapse, when the heart work is dangerously reduced by the insufficient venous return and the cardiac output drops to unsafe figures.

We believe, finally, that the combined use of these two medicaments could constitute a practical method of treatment in cases of cardiac insufficiency by reducing the demands of the organism by about one fourth.

The author wishes to thank Professor P. W. Duchosal, Directeur du Centre de Cardiologie de l'Hôpital Universitaire de Genève, for the very valuable assistance given in the preparation of this paper. He is also grateful to Dr. J. P. Doret, Mr. E. Gay, and Miss S. Juillard for their technical assistance.

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# THE EFFECT OF LANATOSIDE C ON THE CIRCULATORY AND VENTILATORY CHANGES OF CHRONIC RHEUMATIC HEART DISEASE WITH MITRAL STENOSIS

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AN earlier study of the use of lanatoside C in patients with chronic pulmonary diseases demonstrated that the drug had both beneficial and deleterious effects and that often these occurred concomitantly in the same patient.[1] The most consistent effect of lanatoside C in these patients, and one which was assumed to be beneficial, was a rise in the rate of systemic blood flow. Other effects which were considered to be deleterious were a rise in right atrial mean and right ventricular end-diastolic pressures, an increase in functional residual capacity of the lung, and a decrease in arterial blood oxygen saturation.

Since mitral stenosis may impose a burden on the right side of the heart resembling, in some ways, the increased right ventricular work load often seen in chronic pulmonary diseases, it seemed worthwhile to observe the alteration in circulatory and ventilatory function in response to lanatoside C in a group of patients known to have mitral stenosis. The response to lanatoside C also seemed to offer a technique which might be of value in selecting those patients who would benefit from mitral valve surgery. Finally, the action of lanatoside C on the myocardium offers a means of experimentally altering hemodynamic function and thereby demonstrating the effects of valve lesions on blood flow.

For these reasons investigation of the effect of lanatoside C in patients with mitral stenosis, which constitutes the present report, was undertaken. The predigitalization circulatory and ventilatory phenomena associated with this group of patients have been reported previously in a more general study of valvular heart disease.[2]

## METHODS

*Material.*—Six patients from the University service of the Grace-New Haven Community Hospital were the subjects of this study. In each case a reasonably certain diagnosis of chronic rheumatic heart disease with mitral stenosis had been made.

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This work was supported by a grant from the Life Insurance Medical Research Fund.
Received for publication July 13, 1953.

TABLE I. CLINICAL DATA

| CASE NO. | PATIENT | SEX | AGE YR. | AGE OF ONSET YR. | DURATION OF SYMPTOMS YR. | SEVERITY OF SYMPTOMS | HISTORY OF HEMOPTYSIS | SIGNS OF CONGESTIVE FAILURE | VALVE LESIONS | ROENTGENOGRAM | ECG | IMPROVED AFTER LANATOSIDE C ? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | V.M. | F | 32 | ? | 3 | Slight | No | No | M.S. | Marked L.A. and R.V. enlargement | N. | Yes |
| 2. | R.M. | F | 37 | 15 | 5 | Slight | No | No | M.S. | Minimal L.A. enlargement | N. | Yes |
| 3. | A.E. | M | 26 | 15 | * | * | No | No | M.S., M.I. | L.A. and R.V. enlargement, calcific mitral valve | Marked R.A.S.; high, wide & notched p-waves | No |
| 4. | J.V. | F | 25 | 7 | 5 | Slight | No | No | M.S., A.I.?† | Indeterminate | N. | No |
| 5. | P.F. | M | 40 | 10 | 2 | Marked | Yes | Yes | ‡ M.I., M.S. | Marked generalized cardiac enlargement; pulmonary congestion | Moderate R.A.S.; R.V. hypertrophy and strain | Yes |
| 6. | I. W. | F | 46 | ? | 6 | Moderate | Yes | No | M.S., M.I., A.S. | Marked L.A., L.V., R.V. enlargement, pulmonary vessels full, diffuse nodular densities, calcific mitral and aortic valves | N. | No |

*This patient had no symptoms referable to cardiac function; however, he had had subacute bacterial endocarditis with embolic phenomena. At the time of this study he appeared to have been cured of his endocarditis.

†There were no peripheral signs of aortic insufficiency in this patient, and the question of a Graham Steell murmur was raised.

‡This patient came to necropsy at which time calcium was found deposited extensively in both mitral and aortic valves. There had been no clinical evidence of aortic stenosis.

M.S., M.I., A.S., A.I. = Mitral stenosis, mitral insufficiency, aortic stenosis, aortic insufficiency.

L.V., L. A., R.V. = Left ventricle, left atrium, right ventricle.

N., R.A.S. = Normal, right-axis shift.

*Technical Procedures.*—After at least twenty-four hours hospitalization, the special procedures forming the substance of this report were performed. Cardiac catheterization was begun at 8:30 A.M. with the patient in the resting, fasting state, lying supine on a fluoroscope table. After blood samples, respiratory gas samples, and pressure tracings were obtained, 1.4 mg. of lanatoside C was slowly administered intravenously. In each case a digitalis effect was noted on the electrocardiographic tracing within thirty-five minutes after injection. Blood samples and pressure tracings were again obtained one hour after the injection of lanatoside C. Digitalization was then maintained by oral preparations. Patient 1 had similar studies done after being on oral digitalis for 2 years (Case Number 1c in Tables II, III, IV, V).

Right ventricular and brachial artery blood samples were collected while the patient was breathing room air, and, after breathing 100 per cent oxygen for five minutes, a second brachial artery sample was obtained. The blood samples were analyzed for oxygen content by the Ordway modification of the method of Roughton and Scholander.[3] A timed sample of expired air was collected in a Douglas bag before and after digitalization and analyzed for oxygen and carbon dioxide content and from this the minute oxygen consumption and respiratory quotient were calculated.[4] Duplicate analyses by different technicians were done on each blood and respiratory gas sample. In the present study the blood gas determinations checked within ± 0.10 volume per cent, and the respiratory gas anaylses within 0.05 per cent.

Pulmonary function studies were done the day before and again the day after digitalization. These consisted of subdivisions of lung volumes and maximal breathing capacity recorded on a 9-liter bell-type respirometer, and functional residual capacity estimated by a modification of the open method described by Darling and associates.[5]

*Calculations.*—The Fick principle was used for determining the rate of systemic blood flow. The magnitude and direction of blood shunts were calculated by formulas based on the work of Lundsgaard and Van Slyke.[6] The L or "lung" factor (see legend below) was calculated by means of a formula devised by Ordway.[7]

$$1.\quad \dot{Q}b = \frac{\dot{V}O_2}{CaO_2 - C\bar{V}O_2}$$

$$2.\quad \alpha = \frac{CL\bar{c}O_2 - CaO_2}{CL\bar{c}O_2 - C\bar{V}O_2}$$

$$3.\quad L = \frac{(CaO_{2O} - CaO_2) - (TbO_{2O} - TbO_2) - (CbdO_{2O} - CbdO_2)}{TbO_2}$$

In the above, the symbols are used as follows:

$\dot{Q}b$ = Systemic blood flow in liters per minute.

$\dot{V}O_2$ = Total oxygen consumption in c.c. per minute.

$CaO_2$ = Arterial blood oxygen content in volumes per cent × 10.

$C\bar{V}O_2$ = Mixed venous blood oxygen content in volumes per cent × 10.

$\alpha$ = Right-to-left shunt not overcome by breathing pure oxygen expressed as a per cent of the total systemic blood flow. This is a "net" value, being the algebraic sum of all right-to-left and left-to-right shunts.

$CL\bar{c}O_2$ = Pulmonary capillary blood oxygen content in volumes per cent × 10. This value is derived from the expression: $(TbO_2 + CbdO_2 - L\,[TbO_2])$.

L = The per cent of hemoglobin passing through aerated pulmonary capillaries which, due to faulty ventilation or diffusion, is not fully oxygenated while breathing room air but becomes saturated while breathing pure oxygen. The arterial saturation plus L cannot equal more than 100 per cent. That it may appear to do so is the result of using an arbitrary value for dissolved oxygen.

$TbO_2$ = Total corrected blood oxygen capacity in volumes per cent × 10.

$CbdO_2$ = Oxygen physically dissolved in blood in volumes per cent × 10.

Subscript o after $O_2$ refers to functions estimated while breathing 100 per cent oxygen instead of room air. The value of 1.0 volume per cent was used for physically dissolved oxygen during pure oxygen breathing. The reasons for using this low value have been discussed elsewhere.[8]

The mitral valve area was calculated by the formulas of Gorlin and Gorlin.[9]

4. $$MVA = \frac{MVF}{31\sqrt{PC - 5}}, \text{ if}$$

5. $$MVF = \frac{\text{cardiac output in c.c. per minute}}{\text{diastolic filling period in seconds per minute}}.$$

The symbols are used as follows:

MVA = Mitral valve area in square centimeters.

MVF = Mitral valve flow in c.c. per second.

31 = An empirical constant

PC = Pulmonary capillary pressure in mm. Hg

5 = Assumed left ventricular diastolic pressure

The formula described by Aperia was used to calculate the vascular resistances.[10]

6. Resistance in dynes/seconds/centimeters[5]

$$= \frac{\text{Pressure differential}}{\text{Systemic flow, c.c./s.c.c.}} \times 1332.$$

## RESULTS

Four women and two men, ranging in age from 25 to 46 years, were the subjects of the present study. The clinical findings are given in Table I. One patient (Case No. 3) had never had symptoms referable to the cardiorespiratory system, while in the others the duration of such symptoms was from 2 to 6 years. There appeared to be no relation between the duration of symptoms and their severity, although the two oldest patients (Cases 5 and 6) had the most severe symptoms and were the only ones with histories of hemoptyses. Frank signs of congestive failure as indicated by râles in the lung, hepatomegaly, and ankle edema were present in only one patient (Case 5).

TABLE II. BLOOD GAS AND SHUNT DATA

| CASE NO. | | $O_2$ USED C.C./MIN. ($\dot{V}O_2$) | R.Q. | BLOOD $O_2$ CONTENT, VOLUMES PER CENT | | | | | ARTERIAL BLOOD $O_2$ SATURATION (%) | MIXED VENOUS BLOOD $O_2$ SATURATION (%) | $L \times 100$ (% OF $TbO_2$) | $\alpha \times 100$ (% OF Qb) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | AMBIENT ARTERIAL ($CaO_2$) | AMBIENT VENOUS ($C\bar{v}O_2$) | ARTERIAL AFTER BREATHING $O_2$ ($CaO_2o$) | $O_2$ PHYSICALLY DISSOLVED ($CbdO_2$) | CORRECTED $O_2$ CAPACITY ($TbO_2$) | | | | |
| 1. | a | 196 | 0.68 | 17.2 | 11.7 | 19.3 | 0.23 | 18.1 | 94 | 64 | 6.0 | 0 |
| | b | 217 | 0.71 | 17.2 | 12.7 | 19.2 | 0.22 | 18.2 | 93 | 69 | 6.7 | 0 |
| | c | 247 | 0.75 | 16.6 | 11.6 | 18.9 | 0.29 | 16.8 | 97 | 68 | 3.0 | 0 |
| 2. | a | 219 | 0.80 | 15.0 | 10.0 | 16.0 | 0.26 | 15.4 | 96 | 64 | 1.7 | 8.9 |
| | b | 239 | 0.70 | 15.0 | 10.9 | 16.8 | 0.25 | 15.5 | 95 | 70 | 6.8 | 0 |
| 3. | a | 227 | 0.73 | 17.9 | 11.6 | 19.3 | 0.27 | 18.4 | 96 | 63 | 3.6 | 1.6 |
| | b | 235 | 0.77 | 17.0 | 12.7 | 19.8 | 0.22 | 18.0 | 93 | 70 | 7.0 | 0 |
| 4. | a | 244 | 0.83 | 14.4 | 10.8 | 15.8 | 0.33 | 14.4 | 98 | 74 | 2.0 | 0 |
| | b | 244 | 0.88 | 13.6 | 11.1 | 15.8 | 0.23 | 14.3 | 94 | 77 | 6.0 | 0 |
| 5. | a | 290 | 0.90 | 14.5 | 8.3 | 17.9 | 0.17 | 16.5 | 87 | 50 | 13.0 | 0 |
| | b | 340 | 0.83 | 14.5 | 10.2 | 18.2 | 0.14 | 17.9 | 80 | 57 | 15.9 | 14.0 |
| 6. | a | 234 | 0.74 | 17.3 | 11.6 | 20.0 | 0.23 | 18.1 | 94 | 64 | 6.0 | 0 |
| | b | 202 | 0.75 | 16.4 | 11.3 | 19.3 | 0.18 | 18.3 | 89 | 61 | 11.0 | 0 |

a = before lanatoside C; b = after lanatoside C; c = case No. 1 after being on digitalis for 2 years.

Two patients (Cases 1 and 2) had pure mitral stenosis, two (Cases 3 and 5) had mitral stenosis and mitral insufficiency, one (Case 6) had mitral stenosis, mitral insufficiency, and aortic stenosis, and one (Case 4) had mitral stenosis and either slight aortic insufficiency or relative pulmonic insufficiency (Graham Steell murmur). Roentgenographic evidence of cardiac enlargement was present in five of the six patients studied, and in two (Cases 3 and 6) calcification of valves was seen by roentgenograph. No roentgenographic evidence of calcification was seen in Case 5, but at necropsy the mitral valve was found to be densely calcific. Only two individuals (Cases 3 and 5) had right-axis shift of the electrocardiogram. In no patient was a cardiac arrhythmia present at the time of study.

Subjective improvement in symptoms was noted in three patients after lanatoside C. The other three whose symptoms were unaffected included the two individuals with evidence of aortic valve involvement (Cases 4 and 6), and the patient (Case 3) who had had no symptoms of congestive failure. In each case, electrocardiographic changes associated with a digitalis effect developed after the administration of lanatoside C.

The results of respiratory and blood oxygen data before and after digitalization of the six patients are given in Table II. A truly basal metabolic state probably cannot be attained during a cardiac catheterization; however, a relatively "steady state" was maintained as indicated by the normal respiratory quotients which did not change greatly during the procedure. The oxygen consumption increased slightly after digitalization in most cases.

The mixed venous blood oxygen saturation tended to be low (below 70 per cent except in Case 4) at the beginning of the study and in general a slight rise occurred after digitalization, whereas the arterial blood oxygen saturation which changed in the opposite direction was normal in all except one patient (Case 5) and decreased in each case immediately after digitalization. The change in the arterial blood oxygen saturation was not significant in Cases 1 and 2, although in Case 1, it reached a high normal level after two years on digitalis. In most cases the decrease in arterial blood oxygen saturation was a function of an increase in the L factor (proportion of hemoglobin remaining unsaturated because of "lung" factors). Case 5, however, developed a significant $\alpha$ (net right-to-left) shunt after digitalization and the rise in the L factor in Case 2 was almost completely offset by a drop in the $\alpha$ shunt. The two shunts cannot be directly equated since $\alpha$ is expressed as a per cent of systemic blood flow and L as a per cent of total hemoglobin.

Blood flow and valve area data before and after digitalization are given in Table III. The rate of systemic blood flow rose after lanatoside C in all except one patient (Case 6) who, in addition, showed no clinical improvement. There was a slight fall in heart rate in all cases which was associated with a lengthening of diastolic filling time in the first four cases. The stroke volume failed to increase in only one patient (Case 6), the same patient who had no increase in the rate of systemic blood flow. The calculated mitral valve areas varied in either direction after digitalization, but the data are insufficient to establish the degree of change which can be considered significant. There is no

reason to believe that, except perhaps in the greatly dilated heart, the size of the mitral valve would change after digitalization, hence the changes noted probably reflect the error in the method of calculating the mitral valve area. The factors influencing this calculation have been described previously,[2,9] and the ultimate accuracy of the method can only be established after considerable experience.

TABLE III. BLOOD FLOW DATA AND VALVE AREAS

| CASE NO. | | SURFACE AREA SQ. M. | HEART RATE PER MIN. | SYSTEMIC BLOOD FLOW L./MIN. | STROKE VOL. C.C. | DIASTOLIC TIME SEC. | MITRAL VALVE AREA SQ. CM. |
|---|---|---|---|---|---|---|---|
| 1. | a | 1.52 | 77 | 3.56 | 46 | 0.36 | 0.91 |
| | b | | 75 | 4.82 | 64 | 0.43 | 1.27 |
| | c | | 68 | 4.94 | 73 | 0.50 | ? |
| 2. | a | 1.68 | 80 | 4.38 | 55 | 0.33 | 1.89 |
| | b | | 70 | 5.83 | 83 | 0.44 | 2.16 |
| 3. | a | 1.73 | 87 | 3.57 | 41 | 0.42 | 0.62 |
| | b | | 75 | 5.47 | 73 | 0.50 | 0.88 |
| 4. | a | 1.64 | 105 | 6.80 | 65 | 0.32 | 2.18 |
| | b | | 100 | 9.75 | 98 | 0.44 | 2.06 |
| 5. | a | 1.78 | 100 | 4.68 | 47 | 0.42 | 0.57 |
| | b | | 82 | 7.92 | 97 | 0.42 | — |
| 6. | a | 1.50 | 72 | 4.11 | 57 | 0.47 | 0.88 |
| | b | | 70 | 3.96 | 57 | 0.48 | 0.66 |

a = before lanatoside C; b = after lanatoside C; c = Case No. 1 after being on digitalis for 2 years.

The effects of lanatoside C on central and peripheral pressures are given in Table IV. In most cases the atrial pressures rose slightly following digitalization while the right ventricular systolic and diastolic and the pulmonary artery systolic pressures rose considerably. The pulmonary capillary pressure, high in all cases to begin with, rose in only one patient (Case 6) in whom there was also an increase in the pulmonary artery diastolic pressure. After two years on digitalis the right ventricular and pulmonary artery pressures in one patient (Case 1c) reverted toward the predigitalization levels and the right atrial and pulmonary capillary pressures fell below their predigitalization levels. There was a consistent rise in brachial artery pressure in all of the patients except Case 2.

All the calculated vascular resistances (Table IV) decreased after digitalis except in Case 6. In this patient the calculated pulmonary capillary resistance increased so that even though the pulmonary artery resistance decreased, the net result was an increase in total resistance.

TABLE IV. BLOOD PRESSURE AND RESISTANCE DATA

| CASE NO. | | CHEST A-P DEPTH CM. | PRESSURE AT TABLE LEVEL IN MM. HG | | | | | | RESISTANCE IN DYNES CM.$^5$ SEC. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | RT. ATRIUM MEAN | RT. VENTRICLE S/D | PULMONARY ARTERY S/D | PULMONARY ARTERY MEAN | PULMONARY CAPILLARY MEAN | BRACHIAL ARTERY S/D | PULMONARY ARTERY | PULMONARY CAPILLARY | TOTAL |
| 1. | a | 19 | 12 | 58/14 | 55/38 | 45 | 26 | 90/60 | 427 | 585 | 1012 |
| | b | | 17 | 66/10 | 65/33 | 40 | 20 | 100/56 | 332 | 332 | 664 |
| | c | | 7 | 55/7 | 54/27 | 39 | 4 | 100/60 | 567 | 66 | 633 |
| 2. | a | 22 | 11 | 24/10 | 23/14 | 17 | 13 | 89/53 | 73 | 237 | 310 |
| | b | | 8 | 27/11 | 25/13 | 17 | 13 | 73/44 | 55 | 178 | 233 |
| 3. | a | 20 | 12 | 74/14 | 78/40 | 56 | 32 | 110/68 | 538 | 712 | 1250 |
| | b | | 13 | 98/13 | 96/40 | 53 | 32 | 124/68 | 307 | 468 | 775 |
| 4. | a | 21 | 8 | 32/10 | 33/20 | 25 | 14 | 122/52 | 130 | 164 | 294 |
| | b | | 17 | 48/20 | 41/24 | 31 | 17 | 132/58 | 115 | 139 | 254 |
| 5. | a | 22 | 0 | 88/1 | 87/49 | 50 | 44 | 96/55 | 103 | 751 | 854 |
| | b | | 21 | 116/19 | — | — | — | 138/80 | — | — | — |
| 6. | a | 20 | 8 | 62/9 | 61/28 | 44 | 25 | 91/76 | 370 | 486 | 856 |
| | b | | 13 | 82/16 | 77/40 | 55 | 38 | 127/98 | 343 | 767 | 1110 |

a = before lanatoside C; b = after lanatoside C; c = Case No. 1 after being on digitalis for 2 years.

TABLE V. LUNG VOLUME AND VENTILATORY DATA

| CASE NO. | | LITERS | | | | | | LITERS/MIN. | | | RATIO OF BREATHING RESERVE TO MAXIMAL BREATHING CAPACITY |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | TIDAL VOLUME | VITAL CAPACITY | FUNCTIONAL RESIDUAL CAPACITY | EXPIRATORY RESERVE VOLUME | RESIDUAL VOLUME | TOTAL LUNG CAPACITY | RESTING MINUTE BREATHING VOLUME | MAXIMAL BREATHING CAPACITY | BREATHING RESERVE | |
| 1. | a | .321 | 2.716 | 2.29 | 1.161 | 1.129 | 3.845 | 6.9 | 54.4 | 47.5 | 0.87 |
| | b | .425 | 2.705 | 2.74 | 1.202 | 1.538 | 4.243 | 7.3 | 54.4 | 47.1 | 0.87 |
| | c | .363 | 2.384 | 2.39 | 0.798 | 1.592 | 3.976 | 7.3 | 51.8 | 44.5 | 0.86 |
| 2. | a | .384 | 3.234 | 2.16 | 1.140 | 1.020 | 4.254 | 9.0 | 134.7 | 125.7 | 0.93 |
| | b | .342 | 3.400 | 2.31 | 0.933 | 1.377 | 4.777 | 7.5 | 141.2 | 133.7 | 0.95 |
| 3. | a | .456 | 1.689 | 3.44 | 0.622 | 2.818 | 4.507 | 12.7 | 72.6 | 59.9 | 0.82 |
| | b | .539 | 1.368 | 3.92 | 0.238 | 3.682 | 5.050 | 12.6 | 80.3 | 67.7 | 0.84 |
| 4. | a | .425 | 2.425 | 1.92 | 0.643 | 1.277 | 3.702 | 10.2 | 41.0 | 30.8 | 0.75 |
| | b | .373 | 2.208 | 2.73 | 0.643 | 2.087 | 4.295 | 8.2 | 41.0 | 32.8 | 0.80 |
| 5. | a | .612 | 3.338 | 3.71 | 1.435 | 2.275 | 5.613 | 13.0 | 106.0 | 93.0 | 0.88 |
| | b | .518 | 3.180 | 4.43 | 1.358 | 3.072 | 6.252 | 12.0 | 90.0 | 78.0 | 0.87 |
| 6. | a | .332 | 2.674 | 2.38 | 0.954 | 1.426 | 4.100 | 6.5 | 68.6 | 62.1 | 0.91 |
| | b | .425 | 2.695 | 2.53 | 1.026 | 1.504 | 4.199 | 8.9 | 75.1 | 66.2 | 0.88 |

a = before lanatoside C; b = after lanatoside C; c = Case No. 1 after being on digitalis for 2 years.

The lung volume and ventilatory studies done on the six patients are given in Table V. The tidal volumes and vital capacities were within normal limits and varied slightly in both directions after lanatoside C. The low vital capacity and the high functional residual capacity in Case 3 are inexplicable. The patient had no clinical signs or symptoms consistent with these findings. In every case the functional residual capacity and the total lung capacity increased after digitalization. The increase in functional residual capacity was a function of an increased residual volume since the expiratory reserve volume usually decreased (Cases 2, 3, and 5) or remained the same (Case 4). In the two patients (Cases 1 and 6) in whom the expiratory reserve volume increased, the rise was smaller than the rise in residual volume.

The minute breathing volume which was high to begin with changed in either direction after lanatoside C and could not be correlated with clinical symptoms. There did not appear to be a significant change in maximal breathing capacity, which was initially low in all except Case 2. As a result of the variable behavior of the minute breathing volume, the breathing reserve and the ratio of breathing reserve to maximal breathing capacity were also varied.

## DISCUSSION

As in patients with chronic pulmonary disease, in five of the six patients with the heart disease reported here the outstanding effect of lanatoside C was an increase in the rate of systemic blood flow. A rise in the rate of blood flow after digitalis therapy has been reported by others in most types of heart disease.[11-18] Only in individuals with normal hearts does digitalis regularly fail to elicit this response,[19] although variable results have been reported in mitral stenosis with severely impaired pulmonary function.[20]

The observed rise in mixed venous blood oxygen saturation above the low levels found in untreated heart failure, a corollary of the decrease in arteriovenous oxygen difference, might be the result of the increase in the rate of blood flow. The latter would not, however, account for the decrease in arterial blood oxygen saturation which, although slight, was significant in four of the six patients. In three of these four cases the fall in arterial oxygen saturation was related to an increase in the L factor which is a function of the intrapulmonary gas mixing and dispersion factors.[21] It may be significant that the patient (Case 5) who had the greatest fall in arterial blood oxygen saturation had a large increase in the $\alpha$ shunt. A similar but more pronounced response to lanatoside C was seen in two of nine patients with chronic pulmonary disease previously studied.[1]

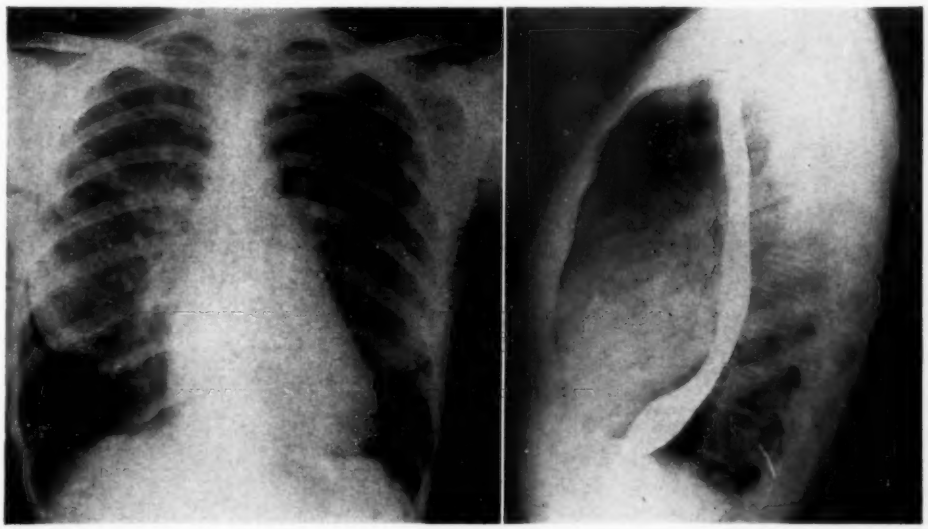
The intrapulmonary $\alpha$ shunt represents the flow of blood through channels inaccessible to ventilation.[6] Although data presently available are insufficient to define these shunts precisely, the four most likely explanations for an increase in the $\alpha$ shunt have been discussed in earlier reports.[1,2] The first of these explanations supposes that at a time when perfusion of aerated capillaries is already maximal because of shunting of blood away from diseased (nonaerated) lung, an increase in output of the right ventricle would result in an inordinate rise in per-

fusion of unaerated as compared with aerated capillaries. The relatively greater perfusion of unaerated capillaries after digitialzation in such circumstances would increase the observed $\alpha$ shunt. A second explanation is based on the observations that have been reported of direct pulmonary artery to pulmonary vein shunts.[22] A rise in pulmonary artery pressure after digitalization might increase the amount of blood shunted through these channels, or, indeed, open such shunts not previously functioning. The final two possible explanations for an increase in $\alpha$ shunt include, first, a decrease in left-to-right shunts through bronchial to pulmonary artery collateral channels (since $\alpha$ is the algebraic sum of the total right-to-left and the opposing left-to-right shunts), and, secondly, the occurrence of blood flow via bronchial veins from the azygous veins to the pulmonary veins. No evidence has been found that collateral bronchial to pulmonary artery channels occur in mitral stenosis. However, the high pulmonary venous pressure of mitral stenosis may result in flow from pulmonary veins to azygous veins via bronchial veins[23] (the direction of flow being opposite that of the bronchial vein mechanism described above), thus acting in much the same way as bronchial to pulmonary artery collateral channels. Then with a rise in right atrial pressure such as observed in some cases after digitalization, this flow might be reversed, leading to an increase in the observed $\alpha$.[24]

The rise in the L factor which is seen in this group of patients after digitalization went hand-in-hand with the rise in pulmonary residual volume, as might be expected since the L factor reflects ventilatory events such as intrapulmonary mixing of gases and the ultimate alveolar oxygen tension. This relationship between changes in the L factor and residual lung volume after digitalization was less clear in a group of patients with chronic pulmonary disease.[1] The present group is small, and an apparent correlation of this sort may be misleading since one is observing but a few factors of many in a complex inter-related physiological system.

The rise in rate of systemic blood flow which is seen in most of these patients after digitalization is similar to previous observations in many diseases[1,11-18] and, except in the normal heart[19] probably should be expected. The failure to show a rise in the rate of systemic blood flow or in stroke volume in Case 6 was singular and deserves further consideration. This patient had very definite electrocardiographic evidence of a digitalis effect at least 30 minutes before the postdigitalis physiological studies were done. Clinically, she did not feel better after digitalization; in fact, she was subjectively worse. This had been observed on several previous attempts at digitalization. Although her clinical course had been marked by considerable dyspnea, orthopnea, and occasional hemoptyses, it had been remarkable for the absence of ankle edema, hepatomegaly, or râles in the lungs. The chest roetgenogram (Fig. 1) was notable for the presence of calification in the region of both the mitral and aortic valves, and more particularly for the widely disseminated nodular densities. These radiological densities have been described in association with pulmonary hemosiderosis deposits.[25] The pulmonary capillary and alveolar wall thickening sometimes found in the lungs of patients with long standing mitral stenosis[26] might also contribute to such roentgenographic

appearance. Another finding of possible significance was the fact that this patient, before digitalization, had a well compensated right atrium and ventricle as judged by pressures. The pulmonary capillary pressure was markedly elevated.



*A.* *B.*

**Fig. 1.—Patient No. 6. Posteroanterior (*A*) and left lateral (*B*) roentgenographic projections showing disseminated nodular densities in the lung fields and calcification of the aortic valve.**

After digitalization the right atrial mean and the right ventricular end-diastolic pressures rose to a level suggesting incipient failure, and the pulmonary capillary pressure rose to an even greater degree. It is tempting to speculate that, in this case, digitalis did, indeed, increase the total output of the left ventricle but that, because of the calcific aortic stenosis, the increase was entirely diverted back into the left atrium through the incompetent mitral valve, thus leaving the "forward" stroke volume unchanged. Whatever the direction of egress, increasing the left ventricular stroke volume involves either an increase in flow from the lungs or a decrease in left ventricular diastolic residual volume. Since the flow from the lungs is determined largely by right ventricular output, in turn limited by flow from the systemic circulation, and since the rate of systemic blood flow did not increase in this patient, there could have been no increase in flow from the lungs. Therefore, in this patient, a decrease in left ventricular residual volume following digitalis might be postulated. Whether or not this speculation is true, it illustrates the possibility that, in the presence of valvular heart disease, the rate of systemic blood flow need not be correlated with the work of the heart.

The ventricular pressures were increased after digitalis in each case indicating greater ventricular work. In contrast to many previous reports,[11,12,14,15] the atrial pressure did not decline in every case, but actually rose in some patients. This increase in right atrial pressure has been observed in cases of chronic cardiopulmonary disease after digitalization,[1] and the cause is not clear. It may, however, be a transient effect, and in the one case studied after prolonged digitalization (Case 1) the right atrial (as well as the pulmonary capillary) pressure fell well below the predigitalization levels.

A considerable change in calculated vascular resistance was noted after digitalization. In most cases there was a pronounced decrease in the pulmonary artery, "pulmonary capillary", and total pulmonary vascular resistance. However, the conclusion that lanatoside C has a specific effect on pulmonary vascular tone is probably not warranted because vascular resistance is not entirely a function of the cross section of the vascular tree but is also influenced by such factors as velocity, laminar versus turbulent flow, and possibly by changes in blood viscosity.

If the immediate postdigitalization period represented a period of generally improved cardiac compensation, then the decrease in expiratory reserve volume and rise in residual volume of the lung observed in this group of patients would be in contrast to the findings of other observers.[27,28] It may very well be that these changes in lung volume reflect the initial rise in pulmonary vascular pressures incident to digitalization. As further physiological readjustments take place, the residual volume might then be expected to decrease.

In general, the immediate results of an effective dose of lanatoside C in the present group of patients with mitral stenosis has been an increase in the work of the heart, thus resembling the observations in a group of cardio-pulmonary patients previously reported.[1] The increased work was manifested by a rise in right ventricular systolic pressure in each case, and a rise in stroke volume in all but one (Case 6). In the latter case aortic stenosis and mitral insufficiency were prominent in addition to mitral stenosis, and this combination of clinical and physiological circumstances may be a clue to the cause of an occasional failure of improvement with digitalization in a decompensated case of rheumatic valvular disease. Furthermore, it seems unlikely that mitral valvulotomy would prove to be of value in this combination of valve lesions when the rate of systemic blood flow does not increase after digitalization. Thus, a rise in the rate of blood flow after digitalization might be used as a criterion for selecting patients for mitral valvulotomy.

In some of the patients of this series the paucity of signs of congestive failure did not preclude a pronounced increase in stroke volume and rate of systemic blood flow following digitalization. Since there was not an accompanying rise in resting oxygen utilization, an increase in cardiac reserve is suggested. Early digitalization may, therefore, serve a useful purpose in the patient with valvular heart disease even though there are few signs of failure and no clinical evidence of improvement follows.

SUMMARY

1. Circulatory and ventilatory studies before and one hour after the administration of an effective intravenous dose of lanatoside C to six patients with chronic rheumatic heart disease and mitral stenosis were reported.

2. Clinical improvement was noted in only three of the six patients.

3. Lanatoside C consistently increased the work of the heart by increasing the right ventricular and peripheral arterial pressures and (except in one case) the rate of systemic blood flow. The reasons for the lack of an increase in the rate of systemic blood flow in one case were discussed.

4. The increased work of the heart seen after lanatoside C in some patients who had neither frank signs of congestive failure nor a clear-cut clinical response to full digitalization was cited as evidence supporting the early use of digitalis in patients with mitral stenosis.

5. In the presence of multiple valve lesions, a rise in the rate of systemic blood flow after digitalization was suggested as a necessary criterion in the selection of patients for mitral valvulotomy.

The authors are indebted to Miss Evelyn Haller, Miss Toby Katz, and Miss Theresa D'Ambrosi for the technical procedures involved in this study.

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# THE SPASMOLYTIC ACTION OF "SOLUBLE KHELLIN—NOKHEL"

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THE object of the observations described in this communication is to compare the spasmolytic and the coronary vasodilator action of natural khellin with that of a water soluble derivative of khellin recently prepared by Deloume-Houdé. The soluble compound is a chlorhydrate of the diethylaminoethyl ether of dihydroxymethyl furo-chromome. This substance is obtainable under the name of "Nokhel" in a form of ampules for intramuscular injections and in tablets in a dose of 50 mg. per ampule and per tablet. The sample of Nokhel at our disposal was obtained from the Laboratories of Houdé in Paris. Chemically pure khellin was used for comparison (m. p. 154°C). It was prepared by extraction from the fruit of *Ammi visnaga* and subsequent crystallization from methanol.

The biological assays were made on the rectal cecum of the fowl and on heart-lung preparations of dogs.

## OBSERVATIONS ON THE RECTAL CECUM OF THE FOWL

This preparation was first used for the assay of khellin by Anrep and associates[1] who found it sensitive to khellin concentrations as low as 0.2 μg/ml.

Table I

| KHELLIN | | NOKHEL | |
|---|---|---|---|
| AMOUNT ADMINISTERED IN μg | RELAXATION OF CECUM IN MM. | AMOUNT ADMINISTERED IN μg | RELAXATION OF CECUM IN MM. |
| 5 | 22 | 5 | 5 |
| 5 | 20 | 10 | 7 |
| 5 | 24 | 20 | 10 |
| 5 | 23 | 40 | 19 |
| 10 | 38 | 100 | 35 |

**Comparative assay of the spasmolytic action of Nokhel and khellin on the rectal cecum of the fowl. The two substances were administered alternately. No correction for the lower magnification has been made.**

and accurate to about 10 per cent. In the present investigation the cecum was suspended in a bath 6 ml. in capacity in aerated Tyrode's solution at 35°C. An example of a comparative assay of Nokhel and khellin is given in Table I from which it can be seen that the equivalent amounts of the two substances were

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Received for publication July 28, 1953.

10 μg of khellin and 100 μg of Nokhel. The spasmolytic action of Nokhel was, therefore, approximately 10 per cent of that of khellin. With different preparations of the cecum this relation varied within narrow limits never exceeding 15 per cent.

### OBSERVATIONS ON THE CORONARY BLOOD FLOW

These were made on three standard heart-lung preparations on dogs. The coronary blood flow was recorded from the coronary sinus. The administration of Nokhel was made at intervals of 5 to 10 minutes and never before the outflow of the blood from the sinus had reached a steady level. The results of the three experiments are given in Table II.

TABLE II

| SUBSTANCE ADMINISTERED | TOTAL AMOUNT ADMINISTERED IN MG. | OUTFLOW OF BLOOD FROM THE CORONARY SINUS IN ML./MINUTE | | |
|---|---|---|---|---|
| | | EXP. 1 | EXP. 2 | EXP. 3 |
| Initial blood flow | none | 72 | 45 | 57 |
| Nokhel | 5 | 75 | — | — |
| Nokhel | 10 | 78 | — | — |
| Nokhel | 20 | 87 | — | — |
| Nokhel | 40 | 104 | 77 | 92 |
| Nokhel | 80 | — | 94 | 126 |
| Khellin | 15 | 220 | 190 | 235 |

**The coronary vasodilator action of Nokhel on the heart lung preparation. The amount of blood in circulation was in each preparation about 500 ml.**

It can be seen from these experiments that the coronary vasodilator action of natural khellin was considerably greater than that of its water-soluble derivative, Nokhel.

Because of the prolonged action of the two substances it becomes difficult to express their relative activity in a numerical way. Khellin had to be administered before the coronary blood flow returned to its initial value. But even so, the difference between the action of the two substances is obvious. Doses of Nokhel as high as 40 mg. increased the coronary blood flow by only 60 per cent, while doses of 15 mg. of khellin caused a further increase by more than 100 per cent.

TABLE III

| SUBSTANCE | MINIMAL EFFECTIVE DOSE (MG.) | DOSE (MG.) CAUSING A 100 PER CENT ACTION |
|---|---|---|
| Nokhel | 5.0 | 60–80 |
| Khellin | 0.4–0.6 | 6–10 |
| Aminophylline | 2.0–2.5 | 30–40 |

**Comparative potency of Nokhel, khellin and aminophylline, as measured by their coronary vasodilator action.**

A large number of previous experiments,[2] in which no other drug besides khellin had been used, have shown that khellin in doses of 15 to 20 mg. increases the coronary circulation in a heart-lung preparation by 150 to 200 per cent.

In conclusion, taking the results of our previous observations on the action of aminophylline[3] we can assess the potency of Nokhel as shown in Table III.

## CONCLUSIONS

1. The spasmolytic and the coronary vasodilator action of the water-soluble khellin derivative Nokhel is considerably inferior to that of natural khellin.

2. The activity of Nokhel when tested on the rectal cecum of the fowl was found to be about 10 per cent of that of khellin.

3. In the heart-lung preparation the coronary vasodilator action of Nokhel was about 10 per cent that of khellin. The action of Nokhel was also found to be inferior to that of aminophylline.

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# Clinical Reports

## ELECTROCARDIOGRAPHIC CHANGES DURING SENSITIVITY REACTION TO PENICILLIN

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BROOKLYN, N. Y.

IN ANIMALS and in man, lesions have been found in the heart and blood vessels following accidental or experimental allergic reactions of varying degree. Such lesions appear in the myocardium, particularly in the subendocardial and subepicardial regions,[1] in the valves, and in the coronary vessels, and bear a striking resemblance to those seen in rheumatic fever and in polyarteritis nodosa.[2,3] The local areas of edema and cellular infiltration produced during hypersensitization can be prevented by the simultaneous administration of Benadryl.[4]

Reports on electrocardiographic changes accompanying these allergic changes are meager. Acute myocardial infarction has followed sensitivity reactions to tetanus antitoxin.[5,6] Gulotta[7] reported flattening and inversion of the T waves in limb and V leads, in a patient in whom urticaria and retrosternal pain followed the administration of tetanus antitoxin, and a return of the tracing to normal within two days after the allergic symptoms disappeared. He also cites six previously reported cases with cardiac complications following tetanus antitoxin injection.

In animals in which anaphylaxis was experimentally produced, atrioventricular conduction delays,[8] depression of the S-T segments, flattening or inversion of T waves,[9] widening of the QRS complexes,[8,10] and arrhythmias have been noted.[10] Histamine injection into human beings also causes depression of the S-T segments and flattening of the T waves, which disappears following the injection of an antihistamine.[11]

With the increasing incidence of sensitivity reactions to penicillin attending its widespread use, it is surprising that more cardiac lesions have not been seen. We are reporting a patient in whom penicillin sensitivity caused changes in the electrocardiogram consistent with a diagnosis of pericarditis.

### CASE REPORT

The patient was a man, aged 43, who was admitted to the Williamsburgh General Hospital on May 29, 1953, with a history of the onset, one week previously, of headache, epigastric cramps and nausea. He was given oral penicillin, and on the next day, diarrhea, nausea, and vomiting ensued. Two days later, he developed swelling of the eyelids, with a burning sensation in the eyes

Received for publication July 21, 1953.

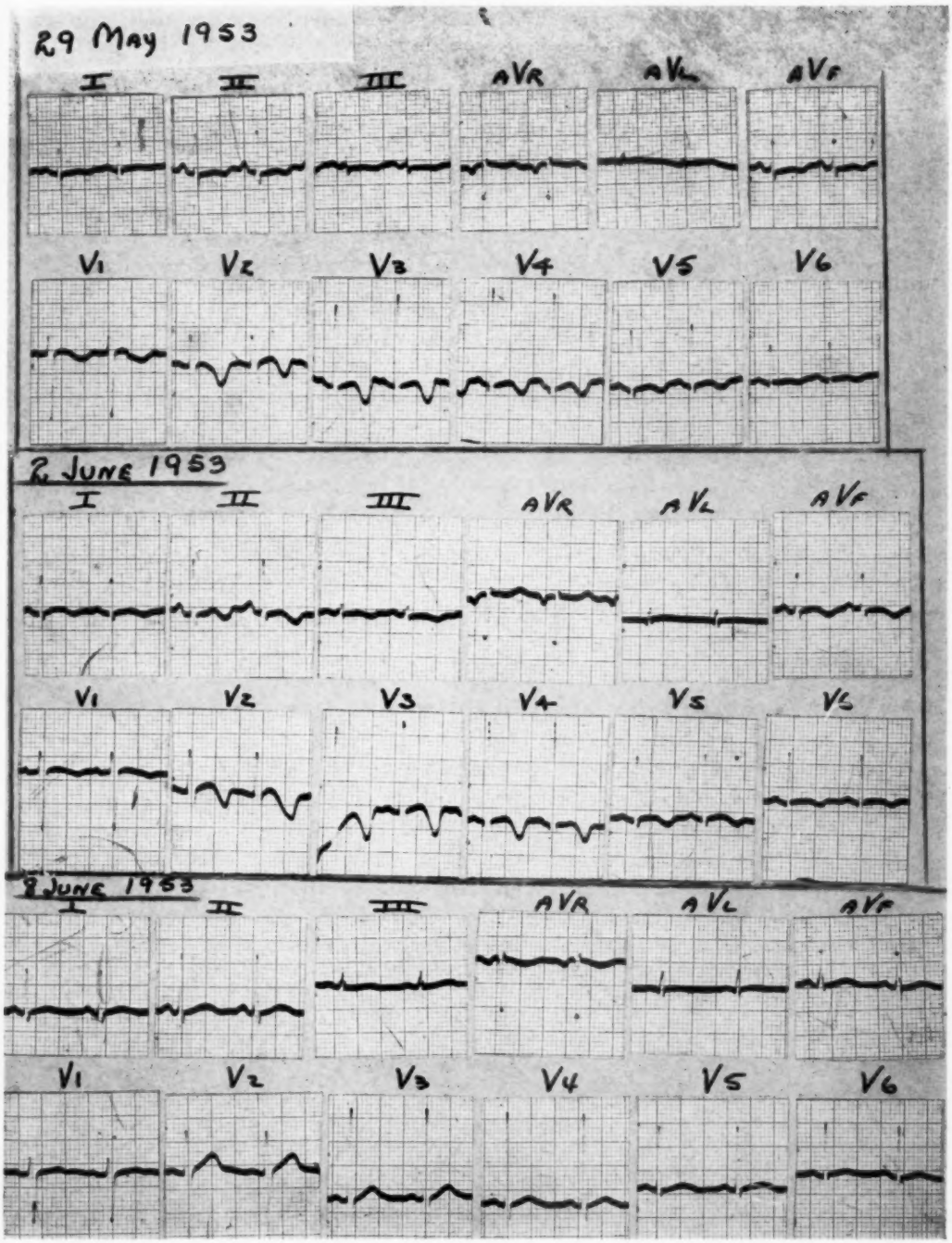


Fig. 1.—Tracings made on May 29 and June 2, show progressive T-wave inversions in limb and precordial leads. The tracing of June 8 was taken after the administration of Chlor-trimeton and is normal.

and penicillin was discontinued. His previous history was entirely negative, and his major complaint was of the swelling and burning sensation around the eyes, some epigastric distress, and a generalized eruption over the body. This rash had been present previously, at intervals, but had reappeared with renewed acuity since penicillin had been administered.

The patient did not appear to be in acute distress and showed no dyspnea. There was slight swelling of the eyelids, with redness of the skin of the entire circumorbital region, redness of the conjunctivae and of the pharynx. The heart was slightly enlarged to the left, rhythm was regular, the rate was rapid. The first apical sound had a slapping quality, but no definite murmurs were heard. The lungs were clear; the liver was palpable and slightly tender. An erythematous, macular eruption was present over the entire body. The temperature was normal.

The urine contained 1 plus albumin, 3 plus acetone, and a number of fine and coarse granular casts. Hemoglobin was 9.5 grams. Red blood cells, 3.4 M.; white blood cells, 7,000/c.mm.; polynuclear cells, 65; eosinophiles, 3; lymphocytes, 32. Blood protein was 5.6 mg. per cent; albumin, 4.0 mg. per cent; globulin, 1.6 mg. per cent. Icteric index, 5; cephalin flocculation a trace. The stool was negative. Roentgenogram showed increased pulmonary markings, with a slightly elongated aortic arch and minimal cardiac enlargement to the left. No signs of pericardial effusion were seen.

An electrocardiogram taken on admission showed inverted T waves in the limb leads and in all the chest leads, as well as in $aV_F$, with a flattened T in Lead $aV_L$. These findings are considered indicative of pericarditis. Treatment was symptomatic, without the use of antibiotics or antihistamines. On June 2, another electrocardiogram showed persistent T-wave inversions in the same leads, with perhaps a greater tendency to inversion. On June 5 treatment was begun with tablets of Chlor-trimeton, 8 mg. every 8 hours. On June 8, after a total of 10 tablets had been given, another tracing was made which showed almost complete reversion of the electrocardiogram to normal, with the exception of persistent flattening of the T wave in Lead $aV_L$.

## DISCUSSION

This case report demonstrates the occurrence of an electrocardiographic pattern consistent with that found in pericarditis, in an individual with no previous cardiac history, and no other etiologic factor than a sensitivity reaction to penicillin administered a short time previously. The prompt return of the electrocardiogram to normal following the use of antihistamine strongly suggests that the entire picture was on an allergic basis rather than an inflammatory one. The mechanism of these changes is not definitely known. It has been suggested that edema of the endothelium and of the media of the coronary vessels, which has been described in anaphylactic reactions, might cause a reduction in blood flow. It is also possible that the myocardial changes, such as edema and cellular infiltration, are diffuse and are located in the subepicardium in a sufficient extent to simulate the pathophysiology of inflammatory pericarditis. The difference lies in the reversibility of the allergic reaction by the use of antihistamines.

A search of the literature brought to light only five cases in whom electrocardiographic changes accompanied sensitivity reactions to penicillin. One patient developed an acute myocardial infarction.[12] In another,[13] slurring of the QRS complex and flattening and inversion of the T waves in the limb leads were observed, with a return to normal within one week on antihistamines. Binder and associates[14] reported three patients with transient changes in the electrocardiogram during allergic reactions to penicillin. These consisted of flattening and inversion of the T waves in the limb and precordial leads, with a return to normal within a short time following antiallergic therapy. Waugh[15] reported the necropsy findings in a patient who died during a hypersensitivity

reaction to penicillin. Although the electrocardiogram did not show any abnormalities, the granulomatous lesions in the myocardium and polyarteritic nodules around the vessels were similar to those reported in the experimental production of allergic cardiac lesions in animals.

## CONCLUSIONS

1. A case has been presented, in whom, during a sensitivity reaction to penicillin, the electrocardiogram showed S-T and T-wave changes consistent with pericardial involvement, and with a complete return to normal within a few days on antihistaminic therapy.

2. A review of the literature produced one case of acute myocardial infarction, and four cases in whom electrocardiographic changes accompanied the allergic reactions to penicillin, with a complete return to normal following antiallergic therapy.

3. The changes in the myocardium, valves, and coronary vessels induced by sensitivity reactions resemble those seen in rheumatic fever and polyarteritis nodosa and may be the cause of the electrical alterations observed.

4. We do not believe that electrocardiographic changes during penicillin reactions are as rare as would appear from this report, but if tracings were made in all cases of severe sensitivity reactions, such changes would be seen more frequently.

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# BIDIRECTIONAL VENTRICULAR TACHYCARDIA DUE TO DIGITALIS POISONING

## Response to Potassium Therapy and Evaluation of Arrhythmia Mechanism

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ALMOST every type of arrhythmia and conduction defect can be caused by digitalis intoxication. The onset of a rapid regular heart rate under digitalis therapy may well represent digitalis intoxication rather than cardiac decompensation. Perhaps the appearance of ventricular tachycardia, or ventricular extrasystoles is one of the more ominous signs of digitalis intoxication. The diagnosis of digitalis intoxication may be extremely difficult because advanced myocardial disease is often responsible for the same type of arrhythmia.

Of all the arrhythmias caused by digitalis intoxication, the so-called bidirectional type, or paroxysmal ventricular tachycardia with rhythmic alteration in direction of the ventricular complexes is most uncommon.[1] There have been thirty-two cases of bidirectional alternating ventricular tachycardia recorded in the literature, most of these associated with severe cardiac damage and digitalis administration.[1]

The investigation of the necessity of a balanced solution of potassium, calcium, and sodium ions dates from Ringer's classical experiment on the frog heart.[2] Cattell and Goodell[3] advanced the theory that the action of digitalis could be explained by alteration of the calcium-potassium ratio in favor of calcium. Freedman and Bine[4] reported inhibition or enhancement of digitalis action by appropriate change of potassium concentration.

Clinically, it is well recognized that conditions associated with a loss of intracellular potassium or resulting in a negative potassium balance may be associated with increased sensitivity to digitalis to the point of toxicity.[5-11] Many investigators[12-14] have reported that digitalis causes a loss of potassium from the heart muscle.

As early as 1930, Sampson and Anderson[15] reported the use of potassium salts in certain cardiac arrhythmias, although there was no correlation between successful therapy and digitalis as the cause. The author did suggest that the administration of potassium salts could differentiate the patient with arrhythmia and without evidence of organic heart disease from those with organic disease,

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Received for publication July 28, 1953.

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since the former did not respond. In 1942 this same author[16] reported that ectopic beats caused by digitalis could be abolished in every instance by the oral administration of potassium salts in doses of 5 to 10 grams. Enselberg and associates[17] became interested in potassium salts therapy after encountering a case of digitalis intoxication in a 58-year-old woman recovering from diabetic acidosis who developed multifocal ventricular extrasystoles which were strikingly abolished by 2 Gm. of potassium chloride orally. This same author gave potassium salts, 2 to 10 Gm., forty times to thirty-four patients with various arrhythmias, mostly associated with digitalis, observing effects in each trial appearing in one-half hour and persisting for at least 4 hours. One patient with bidirectional ventricular tachycardia was successfully treated.[17] Buff reported the successful treatment of eighteen cases of digitalis poisoning with 5 to 10 Gm. doses of potassium chloride during the acute toxic phase and later reducing the dose to 1 Gm., 3 times daily. Twenty-two cases in failure not previously digitalized were given Digoxin, 0.5 mg. 3 times daily, together with potassium chloride, 1.0 Gm. 3 times daily, until a definite level of therapeutic digitalization was obtained, after which they were maintained on dosages of Digoxin and potassium. In this group there were few complications, and patients were more alert in contrast to usual digitalization and sodium restriction. The only contradiction to this therapeutic procedure was the presence of any degree of renal impairment.

Various dosages and routes of administration of potassium salts have been reported in the literature. Although it is said that it is difficult to produce potassium intoxication via oral routes if patients have normal kidney function, toxic results have been observed in doses of 2 to 8 Gm., with the production of auriculoventricular block, ventricular extrasystoles, and auricular standstill. Potassium intoxication may cause symptoms similar to, and even simulating, the electrocardiographic changes produced by digitalis[18-21] and with large dosages paresthesias appear.[22,23]

The case history is presented with the purpose of showing the response to potassium salts of bidirectional ventricular tachycardia due to digitalis poisoning and to discuss the mechanism of this arrhythmia.

## CASE REPORT

J. B., a 54-year-old white man was admitted for the second time to the Buffalo General Hospital on Oct. 16, 1952.

*Present Illness.*—This patient was known to be hypertensive for several years and began having symptoms about two years prior to entrance. He had been told by various physicians that he had rheumatic heart disease, and about two years prior to entrance, he began having nocturnal dyspnea, increased fatigue, and exertional dyspnea. Symptoms progressed and he finally saw a physician. He was started on digitalis and given shots with great improvement for several months. He was admitted to the Buffalo General Hospital for the first time on May 18, 1952, with similar complaints and, after hospitalization, improved sufficiently to be discharged. Figure 1 shows the electrocardiogram at that time. Two weeks before this admission (Oct. 4, 1952), the patient began to have complaints of blurring of vision and yellow spots, dyspnea, weakness, and anorexia with occasional vomiting and diarrhea. His physician had increased the digitalis to 2 to 3 tablets daily.

*Physical examination*: The temperature was 99° F.; pulse rate, 130; respiratory rate 26 per min.; and blood pressure 128/102 mm. Hg. Five months previously it had been 170/100 mm. Hg. The pulse was fast, thready, and difficult to count. He was lying in bed in a semiprone position, pale, dyspneic, anxious, and with beads of perspiration on his forehead. The major findings were confined to the cardiopulmonary system. There were fine râles bilaterally at the lung bases posteriorly, and the heart was markedly enlarged to the left. A tachycardia of 160 per minute with occasional periods of gross irregularity was heard. The rate and rhythm varied from time to time, and occasionally there was pulsus bigeminy.

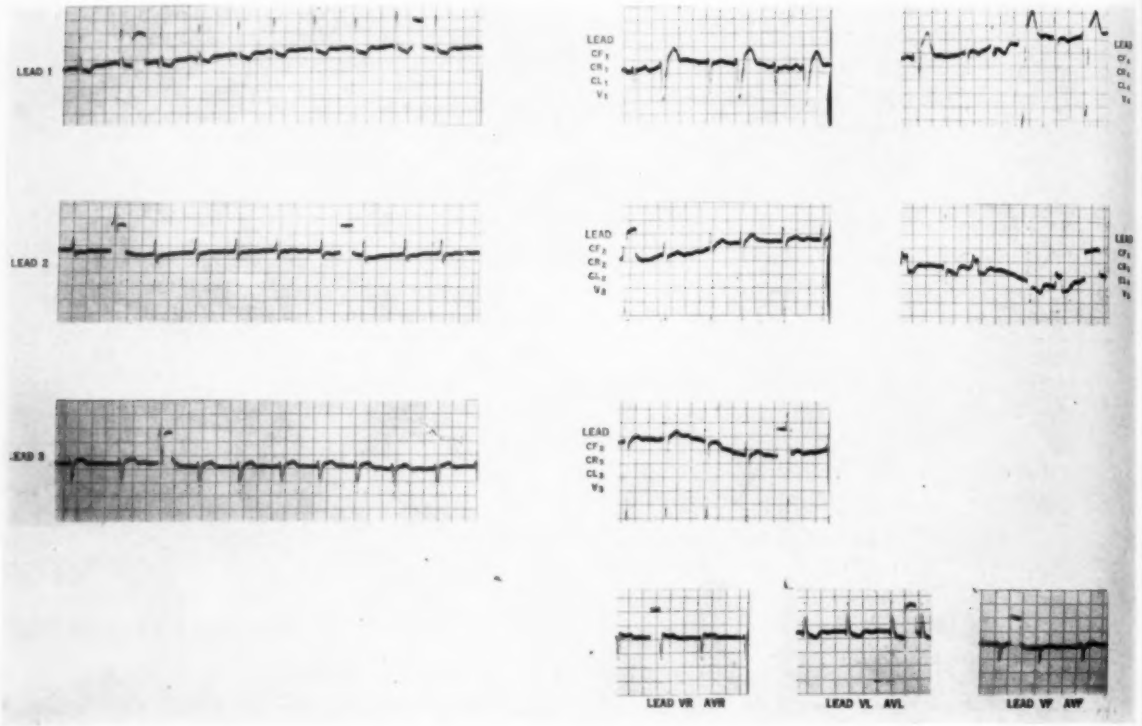


Fig. 1.—Shows electrocardiogram during first admission. Auricular fibrillation and occasional ventricular premature beats are present.

*Laboratory findings*: Red blood count, 5,800,000; hemoglobin, 16.2 grams; white blood cells, 13,000; 8 bands; 70 filaments; 15 lymphs; and 2 eosinophils. A urinalysis showed a specific gravity of 1.014 and a 2-plus albumin. The urea nitrogen was 25 mg. per cent, blood glucose 135 mg. per cent, serum potassium 5.4 meq., bicarbonate 27.6 meq., serum chloride on Oct. 18 was 63 meq., and on Oct. 20 was 100 millieqivalent. The phenosulphonphthalein concentration test was 8 per cent in 2 hours. A serum sodium on Oct. 22 was 138 milliequivalent.

Digitalis was stopped immediately and an electrocardiogram taken (Fig. 2). This showed ventricular tachycardia which later changed to bidirectional tachycardia as illustrated in the first part of continuous tracing. Potassium triplex salts 0.9 Gm. were begun at 3:30 P.M. and 0.9 Gm. hourly thereafter for 6 doses. At 4:15 P.M. the rhythm seemed regular with occasional periods of irregularity. The electrocardiograms taken at that time revealed (Fig. 3) a regular rate, at times resembling a nodal rhythm, short runs of ventricular tachycardia, and escape beats. At 9:00 P.M. the rate and rhythm showed longer periods of regularity, and the patient stated that his yellow vision had improved remarkably. His improvement continued, and on Oct. 23, 1952 potassium

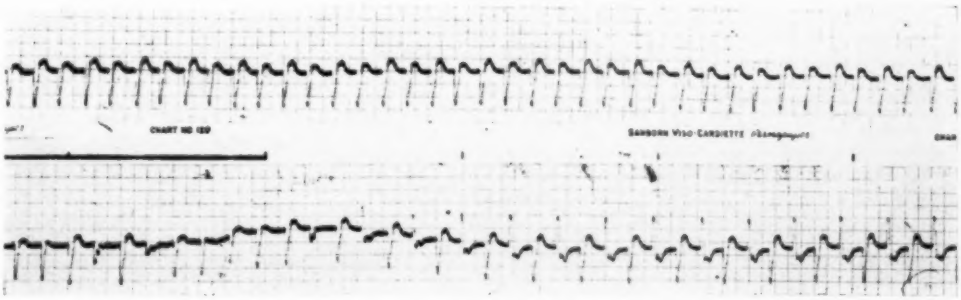

Fig. 2.—Continuous tracing (Lead II) shows ventricular tachycardia changing to the alternating direction of ventricular complexes in the second strip.

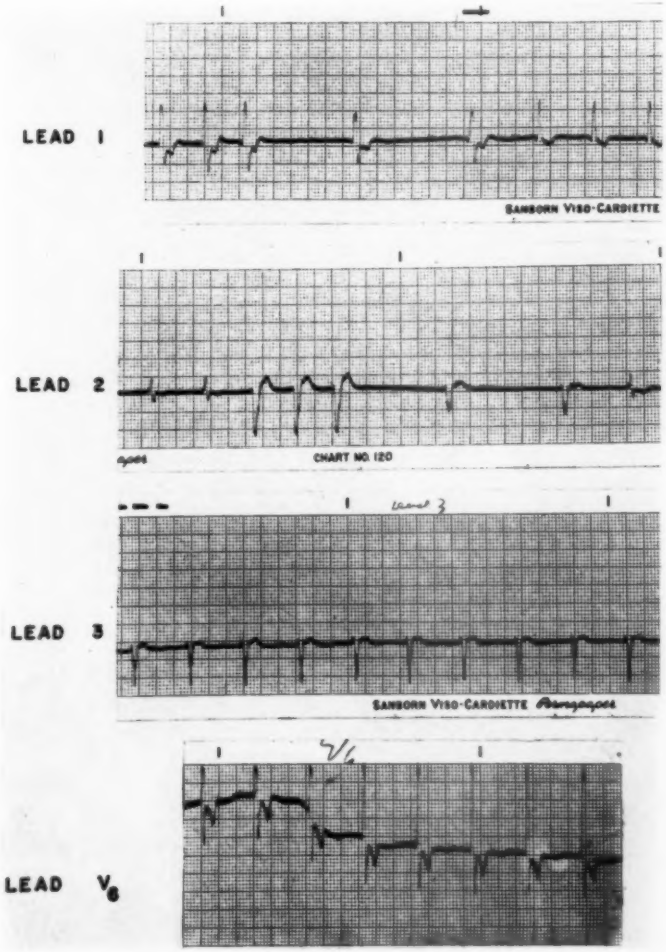


Fig. 3.—Tracing taken approximately one hour after potassium was started orally, shows a regular rate in Lead III resembling a middle nodal rhythm, short runs of ventricular tachycardia, and escape beats.

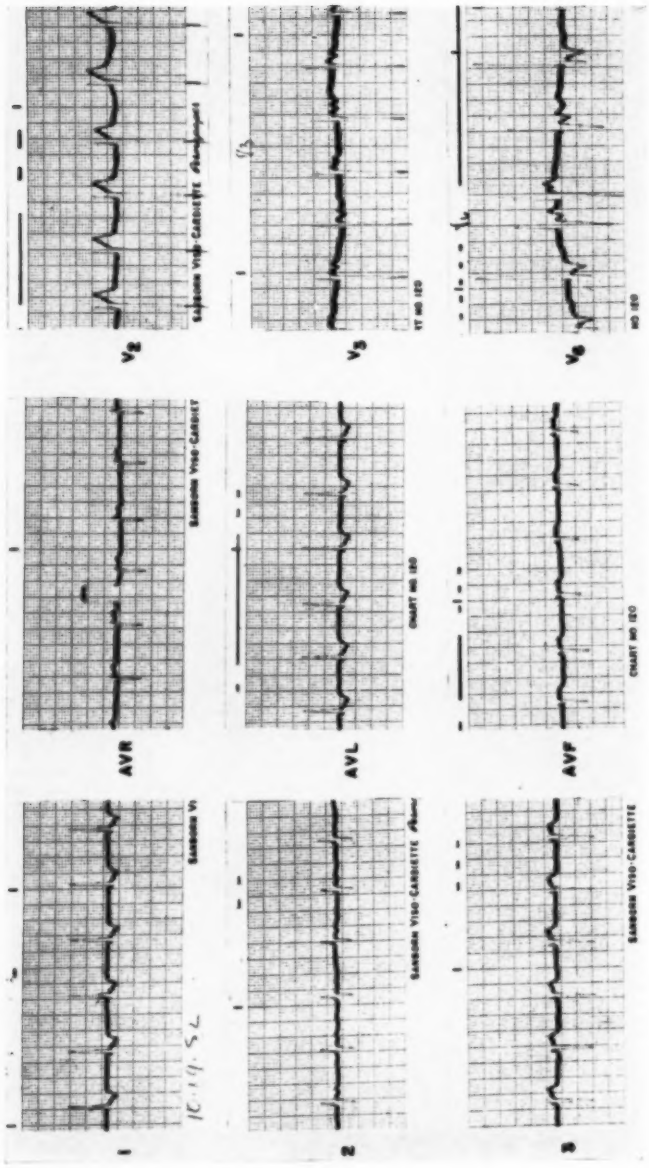


Fig. 4.—Tracing taken Oct. 19, three days later, shows a regular rhythm with only occasional ventricular premature beat.

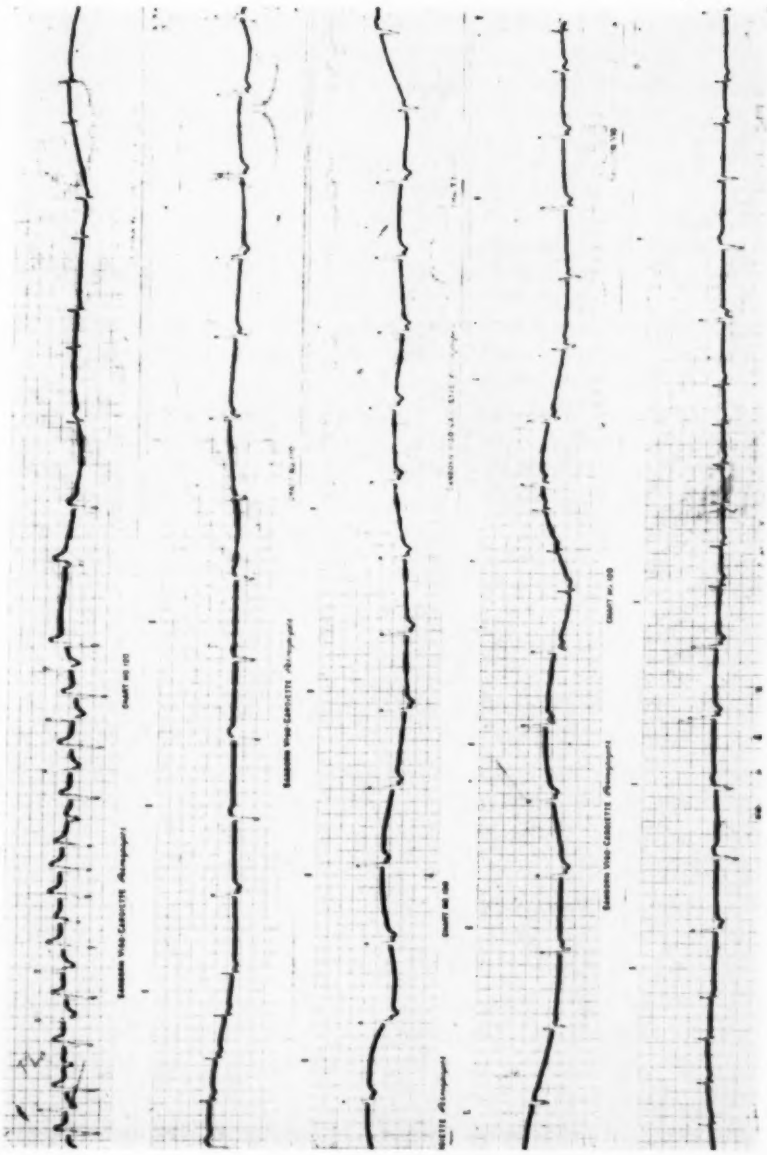

Fig. 5.—Shows effect of carotid pressure. Tracing is a continuous Lead II with carotid pressure exerted during the alternating direction of the ventricular complexes in the first strip. Carotid pressure eliminates the upward complexes, while a few downward directed complexes continue to come before auricular fibrillation appears. In the second, third, and fourth strips both positive and negative complexes appear but do not occur in a regular bidirectional manner. The positive complexes resemble the upward ones of the tachycardia and are probably of nodal origin. The negative ones originate below the bifurcation of the bundle. In the bottom strip, auricular fibrillation is again more apparent. Nodal escape beats still appear at intervals. This picture was repeated with each onset of tachycardia, but the tachycardia could not be stopped permanently until potassium was given.

salts were reduced to 3 times daily. The electrocardiogram taken at intervals until the patient was discharged revealed no return to ventricular tachycardia (Fig. 4). He was discharged on Oct. 30, 1952 with a slow regular pulse, feeling well, and walking about the ward without ill effects.

*Second Admission.*—The patient was admitted to the Chronic Disease Research Institute on Dec. 1, 1952, complaining of marked dyspnea, orthopnea, and marked edema of the extremities and lower abdomen. All of these symptoms gradually had increased since his last discharge from the hospital.

*Physical examination*: Physical examination revealed a markedly dyspneic, pale, anxious white man. The main findings were congestive heart failure with bilateral moist râles in the posterior bases of both lung fields. The liver was markedly enlarged with marked pitting edema of the lower extremities. Blood pressure was 90/60 mm. Hg.

The heart was markedly enlarged to the left with a harsh Grade 3 systolic murmur heard at the apex. The heart tones were of poor quality, and the rhythm was very irregular with an average rate of 80 per minute. An electrocardiogram taken on Dec. 12, 1952 showed auricular fibrillation and frequent ventricular premature beats and was consistent with left heart enlargement. On Dec. 13, there was no change except for fewer premature beats.

The patient was given ammonium chloride and Mercuyhydrin plus a salt-free diet and showed moderate response with less dyspnea and peripheral edema. His weight dropped from 161 to 144 pounds. On Dec. 18, the patient died suddenly.

*Autopsy report*: Chief Diagnosis: rheumatic heart disease. Significant findings were: heart weight 873 grams, old adherent pericarditis, mitral valve measured 13 cm., marked cardiac hypertrophy and dilatation, healed mitral and aorta valvulitis, cor pulmonale, chronic passive congestion of lungs, and congestion of viscera.

## DISCUSSION

In a review, Zimdahl and Kramer[1] noted there had been thirty-one reported cases of bidirectional ventricular tachycardia, and all were associated with severe cardiac damage. To this series they added a case of arteriosclerotic hypertensive cardiovascular disease with bidirectional alternating ventricular tachycardia. Of these thirty-two patients, twenty-seven were receiving digitalis when the arrhythmia occurred. An additional case of bidirectional ventricular tachycardia due to digitalis intoxication responding to potassium therapy was reported by Enselberg and associates.[17]

In none of the other reported cases has it been possible to prove convincingly which type of mechanism is responsible. From the clinical and electrocardiographic evidence in the case reported by Zimdahl and Kramer, it was concluded that there were two separate foci functioning, one in the supraventricular atrioventricular nodal tissue, and the other in the ventricles. Left carotid pressure abolished the complexes thought to be due to foci in atrioventricular nodal tissue; the auricular pacemaker resumed its function, while the ectopic foci in the ventricles still exerted themselves at times.

In this present patient, the same mechanism as postulated by these authors appeared to be responsible for the abnormal rhythm. Figure 5 shows the effect of carotid sinus pressure with the cessation of the alternating ventricular complexes. Later the patient converted to auricular fibrillation which was present prior to the onset of the alternating ventricular complexes. It is interesting to note that most such cases are associated with auricular fibrillation and coupling prior to the onset of abnormal rhythm. It is conceivable that digitalis causes a

high degree of atrioventricular block, leaving some part of the nodal tissue to assume control along with ectopic ventricular foci, producing this abnormal pattern. Because of this response to carotid sinus stimulation, we also feel that there are two separate foci functioning, one in tissue responsive to vagal stimulation, and one in tissues not responsive. We again suggest that this arrhythmia be described as paroxysmal tachycardia with alternating direction of ventricular complexes rather than bidirectional ventricular tachycardia. Several other theories have been advanced to explain the phenomenon of alternating complexes of ventricular tachycardia. Schwenson,[24] Felberbaum,[25] and Luten[26] recognized two possibilities. One was a single focus of origin above the bifurcation of the bundle of His with alternating conduction down the branches; the second possibility was the origin within the ventricles being generated alternately in the right and left ventricle.

The possibility of circus movement in the ventricles as an explanation was first suggested by Gallavardin.[27] Double ventricular circus movement was suggested as an explanation by Palmer and White.[28]

Howard[29] suggested that "the mechanism depends upon a relatively fixed delay in conduction time of one branch of the bundle, while the conductivity of the other branch waxes and wanes so that it alternately exceeds and fails to equal that of the first branch."

## SUMMARY

1. A case of digitalis intoxication with rhythmic alternation in the direction of the ventricular complexes is reported along with electrocardiographic and clinical evidence of improvement following potassium therapy.

2. Clinical and electrocardiographic evidence is presented in this patient which suggests the mechanism was due to the action of two separate foci, one in the atrioventricular nodal tissues above the bifurcation of the bundle of His and the other in the ventricular muscle.

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# INTERVENTRICULAR SEPTAL DEFECT, PULMONARY ARTERY ANEURYSM WITH THROMBOSIS, "CYANOSE TARDIVE," AND PARADOXICAL SYSTEMIC ARTERIAL EMBOLIZATIONS

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THIS case is presented as one whose basic lesion was a large congenital defect of the upper (membranous) portion of the interventricular septum, with the sequence of unusual complications indicated in the title.

## CASE REPORT

The patient, I.C., a textile merchant, consulted one of the authors in 1941, being then 41 years of age. He had known heart trouble since infancy and "bronchial trouble" since the age of eight. His fingers and toes had been clubbed as far back as he could remember. For eight or ten years he had suffered from cough, exertional dyspnea, headaches, tingling in his fingers, and cyanosis.

*Physical Examination.*—The patient was a middle-aged man of medium stature, with a plethoric plum-colored cyanosis. He was not dyspneic at rest but had a frequent, somewhat productive cough. Fingers and toes were markedly clubbed. Chest expansion was normal; there were diffuse moist râles at both lung bases. The heart was moderately enlarged to left and right; there was a marked heave and diastolic shock over the precordium, a loud blowing systolic murmur at the apex, and a short early diastolic murmur heard in the third and fourth intercostal spaces to the left of the sternum. Blood pressure was 125/75 mm. Hg. Liver and spleen were not enlarged; there was no peripheral edema.

Vital capacity at this time was 3.65 liters; maximum breathing capacity 54.8 liters per minute, after bronchodilator spray 68.6 liters per minute. Oxygen capacity was 24.9 volumes per cent, arterial saturation 88 per cent, arterial carbon dioxide content 47.5 volumes per cent.

Diagnoses at this time were: congenital heart disease, probable interatrial septal defect, bilateral pulmonary artery aneurysms, secondary polycythemia, chronic bronchitis.

During the next five years the patient's condition gradually deteriorated, with some increase in palpitation and dyspnea, but he was chiefly troubled with rheumatic pains in neck and shoulder girdle. No cause could be found except for a moderate osteoarthritis. He became increasingly alcoholic. The diastolic murmur along the left border of the sternum varied in intensity, becoming less after prolonged rest. He continued to have a polycythemia and received some transient benefit from phlebotomies. He persistently refused diagnostic study by cardiac catheterization. Roentgenograms of his chest showed gradual increase in size of the heart and the pulmonary aneurysms (Fig. 1).

In 1946, cough, exhaustion, cyanosis, and dyspnea were worse, a systolic murmur developed in the tricuspid area, and his liver was found to be enlarged.

In January 1948, he was in bed several weeks with "pneumonia," chest fluid, peripheral edema. Later in the same year he submitted to a prefrontal lobotomy, because of continuous neck and back pain. This brought no relief.

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Received for publication Aug. 3, 1953.

In 1949, he had a series of episodes of sudden dizziness, weakness, marked dyspnea and cyanosis. Later episodes consisted of abrupt unconsciousness, without warning, in which he would be extremely cyanotic.

In February 1951, he was admitted to the Jewish Hospital in Brooklyn, with fever, severe pain in the right axilla, evidence of consolidation at the right base. He recovered, went home, had a recurrence of the same symptoms followed by the onset of numbness, pain and coldness of the left foot and leg, and was readmitted. The arteries of the left foot were pulseless. There was flatness and bronchial breathing at the right base. Blood cultures were sterile. He developed severe hiccough, relieved only by phrenic nerve resection. On March 11, he developed abdominal pain with vomiting, passed several grossly bloody stools. A diagnosis of mesenteric thrombosis was made. He was considered too weak for operation, was given transfusions, but the abdomen became distended and rigid, and he died on March 13, 1951.

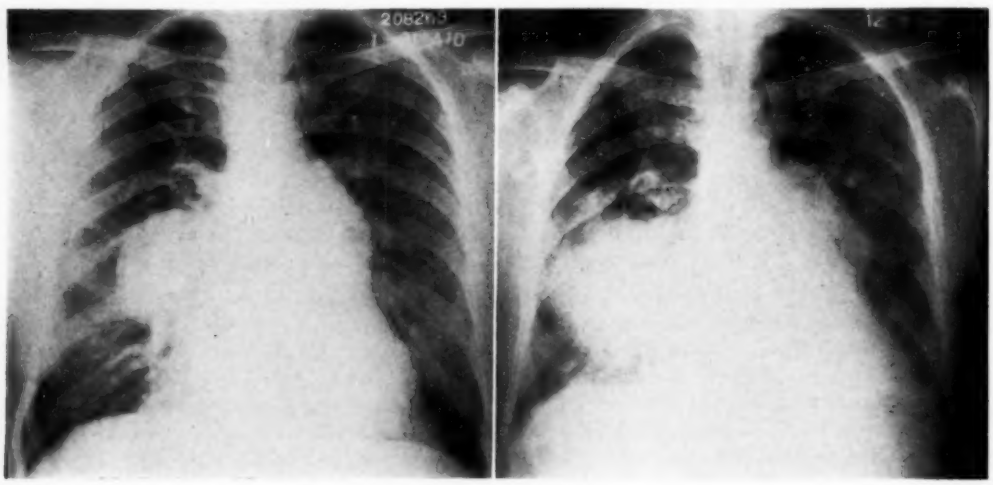

Fig. 1. Fig. 2.

**Fig. 1.—Roentgenogram of chest in 1941, showing pulmonary artery aneurysms and enlarged heart.**

**Fig. 2.—Roentgenogram of chest in 1948. Further enlargement of heart and aneurysms.**

*Autopsy.*—This was performed by Dr. Stanley Sober. The significant findings were as follows:

1. Congenital heart disease, defect in interventricular septum, patent foramen ovale.
(a) Aneurysm of right and left pulmonary artery with thrombosis, infarction of right lung, fibrinous pleuritis and hemothorax, right; (b) Hypertrophy and dilation of heart; (c) Atelectasis, emphysema, congestion of lung.
2. Thrombi in:
(a) Splenic artery with infarct of spleen; (b) Right renal artery with infarct of right kidney; (c) Superior mesenteric artery with infarction of small intestine and fibrinous peritonitis; (d) Left popliteal artery and vein.
3. Arteriosclerosis, general, with particular involvement of:
(a) Coronary arteries, myofibrosis cordis, minute infarcts of heart; (b) Renal arteries with nephrosclerosis.

Necropsy protocol: Heart weight, 541 grams. Epicardium smooth, glistening, transparent. Foramen ovale is patent through valvular slit, 1 cm. in diameter. There is a large interventricular septal defect measuring 2.5 × 2 cm. in membranous part of septum. Endocardium smooth, glistening. Right ventricle dilated. Left ventricle dilated. Tricuspid valve 12.5 cm., thin,

delicate. Mitral valve 12 cm., posterior cusp translucent, anterior cusp opaque. Pulmonary valve 10 cm., velamentous. Aortic valve 8 cm., velamentous, calcification of cusps at base. Myocardium: hypertrophy, firm, red brown color.

The right pulmonary artery is enormously dilated to form an aneurysm measuring 19 × 8 cm. extending from the mediastinum far out into the lung. The pulmonary veins are stretched over its surface. The wall of the aneurysm consists of up to 6 cm. of yellow, tan, and gray lamellated blood clot, and through it is a lumen of about 0.5 cm. in diameter. In places the wall of the aneurysm is calcified. From this aneurysm branches of the artery arise. They are very large and numerous and many are partly or completely occluded by thrombi and have calcific deposits in their walls. The corresponding veins are slightly dilated, but thin-walled.

The left pulmonary artery shows a similar but less severe condition. It measures 8 × 4 cm., calcified in areas, branches greatly enlarged and contain old thrombi.

Main pulmonary artery is dilated, measures 13 cm. in circumference (aorta 7 cm.). Markedly atherosclerotic.

Thickness of left ventricle 2 cm., right ventricle 0.8 cm. Coronary orifices normal, patent; coronaries straight, dilated.

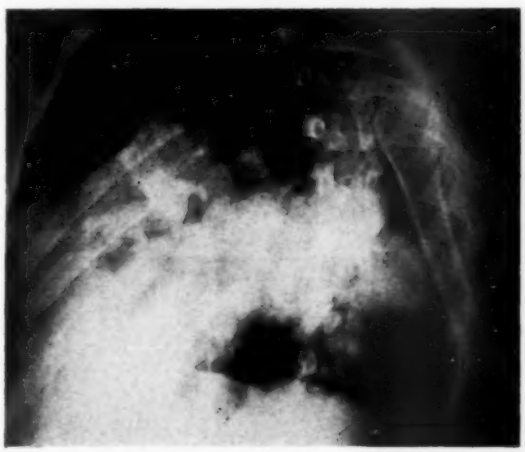

Fig. 3.—Left oblique view of the chest in 1948.

Lungs: Right 1,230 grams, left 640 grams. Right lung pleural surface rough, dull opaque, thickened, generalized adhesions. Anterior surface moist. Infarct soft and liquefying, lower lobe near hilum. Edema, congestion. Left lung: emphysema blebs.

Spleen: 660 grams, red-brown, cut surface purple red. Splenic artery completely occluded by recent thrombus 9 cm. in length. Infarcts up to 7 cm., generalized.

Liver: 1,290 grams, congestion. Some areas of hemorrhage into wall of jejunum. Large intestine: fine fibrinous exudate. Adrenals: 12 grams together. Kidneys: right 130 grams, left 125 grams.

Superior mesenteric artery and branches completely occluded by recent ante-mortem thrombus, loosely adherent to the vessel wall, beginning 3 cm. from the origin of the vessel and stretching for 8 cm.

Right kidney: subscapular infarcts 1 × 0.6 cm.; renal artery, arteriosclerotic.

Aorta: moderate loss of elasticity. Plaques of atherosclerosis mainly in abdominal aorta.

Brain: 1,170 grams. Circle of Willis, arteriosclerotic.

Left popliteal artery and vein completely obstructed by ante-mortem thrombi, adherent to wall of vessels.

Fig. 4.—The heart at autopsy. Upper right marker points to the patent foramen ovale, lower left marker to the large interventricular septal defect, as seen from the left ventricle.

Fig. 5.—Heart and pulmonary artery aneurysm. Below is shown the right ventricle and (marker) interventricular septal defect; above, the large pulmonary artery aneurysm, filled with laminated thrombus.

*Microscopic*: Heart: The epicardium is a thin fibrous layer overlying a small amount of fat. The myocardial fibers are large and their nuclei have considerable variation in size. The myofibrils are distinct. The interstitial fibrous connective tissue is more conspicuous than usual, and in some places forms small sheets replacing muscle fibers. Endothelium normal.

Pulmonary artery main stem: intima smooth but greatly thickened by dense fibrous tissue which in places forms a fairly dense network and in some areas is impregnated with calcium. The elastic intima is almost obliterated. The media is fairly narrow and has much replacement of the muscle fibers with fibrous tissue. It contains numerous small thin-walled blood vessels, especially in the outer half. The elastic tissue in the media is fragmented and deficient in many areas. The adventitia is composed of dense fibrous tissue.

Right lung and aneurysm of right pulmonary artery: The walls of the arteries are composed of a thick layer of granular eosinophilic thrombus. It is impossible to distinguish where the thrombus ends and intima begins. The medial coat is very thin in places, and the outlines of muscle cells and their nuclei are blurred. The adventitia is densely fibrous, with many small groups of lymphocytes and polymorphonuclear cells. The elastic tissue is markedly frayed and deficient. There are large deposits of calcium in the walls of the vessels.

Within the right lung parenchyma the blood vessels are prominent, large, and numerous. They have thick fibrous walls and many are partially or completely occluded by thrombus in varying stages of organization, including recanalization. The alveoli are nearly all collapsed and contain some eosinophilic granular material and large mononuclear cells. In some large areas the cell outlines are lost and only the ghost of the architecture remains. Pleura markedly thickened.

Left lung like right, but many alveoli aerated while some are distended and communicate with adjacent ones to form emphysematous spaces. No infarcts.

Spleen: Many larger arteries filled with ante-mortem thrombus. Infarcted areas.

Kidneys: Infarcted areas, adjacent medium-sized arteries partly filled with ante-mortem thrombus.

Vertebral body: The long trabeculae are mostly narrowed and contain well-marked haversian systems. The intervening spaces are heavily packed with cellular bone marrow containing many erythropoietic cells together with leucopoietic cell series and megakaryocytes. There is little fat present.

## DISCUSSION

The major anatomic lesion in this patient's heart was the large 2.5 × 2.0 cm. interventricular septal defect. This obviously led to a large left-to-right shunt, increase in pulmonary blood flow, with progressive dilatation of both pulmonary arteries. The patent foramen ovale probably played a minor part in this process.

It is possible that the late episodes of "cyanose tardive" were due to right-to-left shunt through the interatrial passage, but this seems unlikely, since the patient was not in any appreciable degree of right-sided congestive failure during at least the early phases of this development. The right ventricle at this time was greatly hypertrophied, and the progressive increase in pulmonary artery thrombosis and in pulmonary embolism might well have provided enough resistance to raise the right ventricular pressure temporarily above that of the left ventricle.

So far as the paradoxical embolisms are concerned, again one cannot prove that emboli may not have passed from a peripheral venous thrombus through the patent foramen ovale; but a more likely course would be that some emboli from the pulmonary artery thrombi dropped through the dilated pulmonic valve, then through the septal defect into the systemic circulation.

Taussig[1] records the incidence of large pulmonary artery aneurysms secondary to high interventricular septal defect, with cyanosis due to pathologic changes in the lungs.

Paradoxical emboli are recorded chiefly by way of a patent foramen ovale or interatrial septal defect (Beattie,[2] Thompson and Evans,[3] Johnson[4]). Birch[5] reported the case of a boy of eleven, in whom a large vegetation from a tricuspid valve passed through an interventricular septal defect.

## SUMMARY

A case is presented of a large interventricular septal defect, patent foramen ovale, pulmonary artery aneurysms, pulmonary artery thrombosis, with both direct pulmonary and indirect "paradoxical" systemic embolization.

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## ANNOUNCEMENT

Dr. Samuel A. Levine, Clinical Professor, Harvard University Medical School, Boston, will take part in a CONTINUATION COURSE IN CARDIOVASCULAR DISEASES FOR GENERAL PHYSICIANS which will be presented at the Center for Continuation Study on the University of Minnesota Campus March 22 to 24, 1954. The course, sponsored jointly by the University and the Minnesota Heart Association, will stress management of practical problems in the cardiovascu'ar field. Dr. Levine will also present the annual George E. Fahr lecture on March 23. The course will be presented under the direction of Dr. C. J. Watson, Professor and Head, Department of Medicine, University of Minnesota Medical School, and the remainder of the faculty will include clinical and full-time members of the faculty of the University of Minnesota Medical School and the Mayo Foundation. Lodging and meal accommodations are available at the Center for Continuation Study.

# Book Reviews

THE PATHOGENESIS AND TREATMENT OF THROMBOSIS, With a Clinical and Laboratory Guide to Anticoagulant Therapy. By Irving S. Wright. New York, 1952, Grune & Stratton, Inc.

The magnitude of the problem of intravascular thrombosis, from the standpoint both of morbidity and mortality, is well recognized today. This recognition, plus the availability of therapeutic techniques for lessening the hazard, has promoted renewed laboratory interest in the mechanisms involved in clotting and in possible means of influencing these mechanisms. Physicians who have been unable to keep up with the very large number of important publications along this line will welcome the opportunity to read Dr. Wright's concise volume. The clarity of the author's thought processes, his teaching ability, and his wide experience in the laboratory and at the bedside of patients with clotting tendencies have combined to provide a very readable and valuable monograph.

The earlier sections deal with the biochemical, physical-chemical, and morphologic aspects of blood clotting in such a fashion as to give the practitioner a brief, but adequate, view of recent developments in the understanding of the basic processes involved. After this there are brief considerations of familial thrombosing tendencies, clotting tendencies in the individual, cryoglobulinemia and cold hemagglutinins, and the influence of ACTH and cortisone on blood coagulation. The latter part of the book then deals with the methods of combating thrombosis, including an excellent discussion of the newer anticoagulants. A very valuable appendix provides a clinical and laboratory guide to anticoagulant therapy.

This book is highly recommended to all physicians using anticoagulant therapy.

T. D.

THE BALLISTOCARDIOGRAM, A Dynamic Record of the Heart Beat. By John R. Braunstein, M.D., Ph.D. Springfield, Illinois, 1953, Charles C Thomas, 83 pages, price, $3.00.

This monograph presents a brief, lucid picture of ballistocardiography from its earliest beginnings in 1877 until 1951, when the material was presented as two lectures at the University of Cincinnati. The volume accomplishes the aim of acquainting the general medical reader with the field without attempting to be a textbook of instruction.

The types of instruments and their physical characteristics, normal and abnormal patterns, and determinations of cardiac output are covered in a manner which, in general, avoids the overenthusiasm of most writers. However, the suggestion of the grave prognostic significance of an abnormal pattern should be tempered until further data are available. More space should be devoted to the differences in pattern obtained with the various instruments employed. The subject of vectorballistocardiography is introduced with a description and schematic diagram for the ballistovectorscope. The actual pictures of the amplifier and oscilloscope could well be omitted from a text of this size.

The idea of presenting some simple definitions in the appendix is to be commended, but inclusion of the various mathematical equations involved in the theoretical considerations seems out of place in a monograph prepared for the general medical reader. J. A. L. M.

A PRIMER OF CARDIOLOGY. By George E. Burch. Second edition, revised. 214 illustrations, 339 pages. Philadelphia, 1953, Lea & Febiger.

A "primer" has been defined as "an elementary text book". Dr. Burch's volume is able to qualify under this definition, but it is much more than just this. For the medical student in his clinical courses, fresh as he is from the laboratories of physiology and pathology, study of this book will serve as a splendid means of applying the basic science teachings to the cardiologic

problems that face him. In this respect it is indeed a "primer". But the graduate physician, wide though his clinical experience may be, very frequently needs a reorientation of his knowledge on a good solid framework of basic understanding. Here also Dr. Burch has fulfilled a very real need.

The second edition uses the same plan of presentation as did the first. Illustrations employed in the latter have been improved and new ones added, and all of them are excellent. There has been an extension of the discussion of congenital heart disease, with emphasis on the current method of clinical study and management, and the treatment section has been expanded (though still relatively brief). Newer developments in other sections have been added also. No bibliography has been included since this is not considered as belonging in a primer. Some objection might be raised to the inclusion of so-called arteriosclerotic heart disease under "Heart Disease Produced By the Aging Process" in view of the mounting evidence in recent years relative to vital metabolic factors, but this is a controversial matter, and Dr. Burch has wisely avoided attempting to present both sides of such questions.

This book is heartily recommended to beginners in cardiology and to all other physicians who wish a reorientation of their knowledge based on the newer developments in the field of cardiovascular physiology. Dr. Burch is to be congratulated for a job very well done.

T. D.

BALISTOCARDIOGRAFIA CLINICA. By D. Sibilia Roma, 1953, Società Edizioni Mediche, 105 pages and 27 figures.

This monograph collects in a concise and clear presentation the various contributions dealing with ballistocardiography, including several by the author himself. Ballistocardiographic techniques are described. Among them, the direct and the indirect methods, and the optical, magnetic, and piezoelectric devices are discussed. Longitudinal, transverse, and sagittal ballistocardiograms are described. In general, the ballistocardiogram is studied more from the point of view of changes of the single waves than as a method for determination of output or ejection.

The various physiologic types of tracing are discussed. In particular, clear schemes point out the differences between the tracing of the "vertical" heart and that of the "horizontal" heart. Functional tests and respiratory variations are described. The second part of the book is devoted to clinical abnormalities with special regard to coronary heart disease. In the evaluation of the clinical value of ballistocardiography, the author shows critical sense and moderation. The final paragraph is devoted to the future of the method which is considered as important.

This book represents a useful compendium and may be employed for consultation. The edition is excellent; the illustrations are good.

A. A. L.

FONOCARDIOGRAFIA CLINICA. By A. Caniggia. Torino, 1953, Edizioni Minerva Medica, 290 pages and 232 illustrations. Lire 3,000.

This monograph of clinical phonocardiography represents the result of a great effort made with singularly inadequate and obsolete technical means. The author is using an electrical method of recording; the microphone is connected with an ink-writing galvanometer. As a result, the electrocardiogram and phonocardiogram are traced as sections of two superimposed arcs.

While the film speed is inadequate (25 mm. per second), any direct-writing instrument has a too low period of vibrations for an accurate sound tracing. Therefore, the various graphs transcribed by the author represent only an interesting technical curiosity. Little exception can be taken to most of the statements of the book. However, there are no quotations, and no bibliography is given in order not to "overload the book" (see foreward by Prof. Izar). Therefore, it is often difficult to know whether the author actually saw the described phenomena or whether he is quoting from published works.

It is a pity that a gifted person, like the author, should try to accomplish so much with so little.

The edition is good, and the tracings are well reproduced

A. A. L.